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CHARACTERIZATION AND LONG-TERM TREATMENT OF FEMALE URINARY INCONTINENCE IN PORTUGAL

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CHARACTERIZATION AND LONG-TERM TREATMENT OF FEMALE URINARY INCONTINENCE IN PORTUGAL

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ABSTRACT

Urinary incontinence, defined as involuntary urine leakage, is a prevalent condition among women, classified into stress, urgency, and mixed urinary incontinence. Global studies estimate a high prevalence, with stress urinary incontinence being the most common subtype, though patterns shift with age. The burden of the condition extends beyond physical symptoms, encompassing psychological, economic, and environmental impacts. This thesis examines the epidemiology, and treatment outcomes of urinary incontinence, with a focus on Portugal.

In Portugal, the prevalence of female urinary incontinence is poorly investigated. This thesis provides the first comprehensive assessment, identifying a nationwide prevalence of 9.9%, with a significant increase with age: from 2.0% in women aged 18–39 years to 28.9% in those aged 75–85 years. Urinary incontinence prevalence decreased with higher levels of education, from 28.2% among women with no formal education to 2.2% in those with more than 12 years of education. Similarly, prevalence declined with rising household income, dropping from 14.4% in the second income quintile to 5.3% in the fifth quintile. It is also significantly associated with comorbidities, such as hypertension, obesity, diabetes, and depression. Many women rely on coping strategies and solutions like pads, without seeking medical treatment due to stigma or lack of awareness. These findings highlight the need for targeted public health initiatives focusing on education, early diagnosis, and access to care.

Being stress urinary incontinence the most common subtype, it is important to guarantee that after failed conservative measures, women have access to effective surgical treatments. These treatments should not only be effective but also easy to perform so that they can be widely available. In an effort to further simplify the surgical technique while reducing the amount of synthetic material used in the standard mid-urethral slings, single-incision slings were introduced. However, their long-term efficacy data is limited. To address this gap, this thesis analyzes long-term success of mini-slings. Our research analyzed mini-slings outcomes over 10 years, reporting an overall cure rate of 47%. Patient satisfaction remained high, with 71.4% of women reporting mild or no symptoms, and 80% expressing willingness to

undergo surgery again. Single-incision mini-slings offer long-term efficacy through a procedure with higher simplicity and reduced morbidity. They may provide greater value for specific groups, such as relatively young and older women. For these reasons, mini-slings should remain a vital option in the surgical arsenal for stress urinary incontinence.

In what concerns to urgency urinary incontinence, conservative measures often fail to achieve sustained adherence or efficacy in real-world settings. Furthermore, increasing evidence of the potential cognitive risks associated with antimuscarinic drugs underscores the need for alternative treatments. In this context, this thesis analyzes the long-term outcomes of botulinum toxin A bladder injections in women with idiopathic urgency urinary incontinence in a real-life scenario, assessing its efficacy and factors influencing treatment outcomes. Our study emphasizes the efficacy of botulinum toxin A, with 74.5% of patients achieving complete dryness and a significant reduction in pad usage after each treatment. Key predictors of treatment success included baseline pad usage and history of sling placement. Higher baseline pad usage was associated with reduced efficacy, while patients without a history of sling surgery demonstrated better outcomes. Repeated injections were administered in 60.3% of cases, with a median of one additional treatment and a median interval of 18 months between the first and second injections. Patient satisfaction with the initial treatment was a strong predictor of repeat injections. Women receiving multiple injections were also younger at diagnosis compared to those who did not pursue additional treatments. Complications were minimal, and easily manageable. Botulinum toxin A is cost-effective, minimally invasive, and particularly suitable for middle-aged or older women within the Portuguese context.

By addressing gaps in knowledge, this thesis provides relevant insights into the epidemiology and treatment of urinary incontinence in Portugal. It emphasizes the importance of personalized care, long-term treatment efficacy, and equitable healthcare access. These findings aim to enhance patient outcomes, reduce societal costs, and inform policies that promote sustainable, effective urinary incontinence management.

RESUMO

A incontinência urinária, definida como a perda involuntária de urina, é uma condição prevalente entre as mulheres, sendo classificada em três subtipos principais: incontinência urinária de esforço, de urgência e mista. Estudos globais estimam uma elevada prevalência, destacando a incontinência urinária de esforço como o subtipo mais comum, embora os padrões variem com a idade. O impacto desta condição vai além dos sintomas físicos, abrangendo consequências psicológicas, económicas e ambientais. Esta tese analisa a epidemiologia e os resultados terapêuticos da incontinência urinária, com foco em Portugal.

Em Portugal, a prevalência da incontinência urinária feminina tem sido pouco investigada. Esta tese apresenta a primeira avaliação abrangente, identificando uma prevalência nacional de 9,9%, com um aumento significativo associado à idade: de 2,0% em mulheres entre os 18 e 39 anos para 28,9% em mulheres entre os 75 e 85 anos. A prevalência diminui com níveis mais elevados de educação, de 28,2% entre mulheres sem educação formal para 2,2% em mulheres com mais de 12 anos de escolaridade. Similarmente, observa-se uma redução com o aumento do rendimento familiar, de 14,4% no segundo quintil de rendimento para 5,3% no quinto quintil. A condição está significativamente associada a comorbilidades, como hipertensão, obesidade, diabetes e depressão. Muitas mulheres recorrem a estratégias de adaptação, e a soluções como o uso de pensos absorventes, sem procurar tratamento médico devido ao estigma ou à falta de conhecimento. Estes resultados destacam a necessidade de iniciativas de saúde pública direccionadas para a educação, diagnóstico precoce e acesso ao tratamento.

Sendo a incontinência urinária de esforço o subtipo mais comum, é crucial garantir que, após o insucesso de medidas conservadoras, as mulheres tenham acesso a tratamentos cirúrgicos eficazes. Estes tratamentos devem não só ser efectivos, mas também simples de realizar, para que possam ser amplamente disponíveis. Neste contexto, foram introduzidos os *slings* de incisão única com o objectivo de simplificar a técnica cirúrgica e reduzir a quantidade de material sintético utilizado nos *slings* tradicionais. Contudo, os dados sobre a sua eficácia a longo prazo são limitados. Para colmatar esta lacuna, esta tese analisa o sucesso a longo prazo dos

mini-slings, revelando uma taxa de cura de 47% após 10 anos de seguimento. A satisfação das doentes manteve-se elevada, com 71,4% a relatarem sintomas leves ou inexistentes e 80% a expressarem disposição para realizar novamente a cirurgia. Os *mini-slings* oferecem uma eficácia a longo prazo com simplicidade cirúrgica e menor morbilidade, sendo especialmente vantajosos para mulheres mais jovens e mais idosas. Por estas razões, devem continuar a ser uma opção essencial no arsenal terapêutico para a incontinência urinária de esforço.

No que respeita à incontinência urinária de urgência, as medidas conservadoras frequentemente falham em alcançar uma adesão ou eficácia sustentadas em contextos reais. Além disso, a evidência crescente sobre os potenciais riscos cognitivos associados aos fármacos antimuscarínicos reforça a necessidade de tratamentos alternativos. Neste âmbito, esta tese analisa os resultados a longo prazo das injecções de toxina botulínica tipo A em mulheres com incontinência urinária de urgência idiopática, avaliando a sua eficácia e os factores que influenciam os resultados do tratamento. O estudo realça a eficácia da toxina botulínica tipo A, com 74,5% das doentes a alcançarem continência total e uma redução significativa no uso de pensos após cada tratamento. Os principais preditores de sucesso incluíram o uso inicial de pensos e a ausência de história de cirurgia com *slings*. Mulheres com um maior uso inicial de pensos tiveram uma menor eficácia, enquanto doentes sem cirurgia prévia apresentaram melhores resultados. Injecções subsequentes foram realizadas em 60,3% dos casos, com uma mediana de um tratamento adicional e um intervalo mediano de 18 meses entre as injecções. A satisfação inicial foi um forte preditor de repetição do tratamento. As complicações foram mínimas e facilmente geridas. A toxina botulínica tipo A é uma opção custo-efectiva, minimamente invasiva e particularmente adequada para mulheres de meia-idade ou idosas no contexto português.

Ao abordar lacunas de conhecimento, esta tese fornece contributos relevantes para a compreensão da epidemiologia e do tratamento da incontinência urinária em Portugal. Enfatiza a importância de cuidados personalizados, eficácia terapêutica a longo prazo e equidade no acesso à saúde. Estes achados visam melhorar os resultados clínicos, reduzir os custos para a sociedade e contribuir

para políticas que promovam uma gestão sustentável e eficaz da incontinência urinária.

ABBREVIATIONS

AUS	Artificial urinary sphincter
CIC	Clean intermittent catheterization
EAU	European Association of Urology
EU	European Union
MUI	Mixed urinary incontinence
MUS	Mid-urethral slings
OAB	Overactive bladder
PFMT	Pelvic floor muscle training
PGI	Patient Global Impression
P-PTNS	Percutaneous posterior tibial nerve stimulation
PTNS	Posterior tibial nerve stimulation
SUI	Stress urinary incontinence
SNM	Sacral neuromodulation
T-PTNS	Transcutaneous posterior tibial nerve stimulation
UI	Urinary incontinence
UK	United Kingdom
UTI	Urinary tract infection
UUI	Urgency urinary incontinence

INTRODUCTION

Urinary Incontinence, Prevalence and Economic Burden

Urinary incontinence (UI) is the complaint of any involuntary leakage of urine. It can be categorized as stress UI (SUI), when the leakage occurs on effort, exertion, on sneezing or coughing; or urgency UI (UUI) when the leakage is accompanied by or immediately preceded by urgency. It can also occur in both situations, being termed mixed UI (MUI) [1].

Different studies report female UI prevalence, with most of them estimating a percentage between 25 and 45% [2]. In 2003, a study with women from France, Germany, Spain, and the United Kingdom (UK) reported a 35% overall prevalence of self-reported involuntary loss of urine in the preceding 30 days [3]. The Epidemiology Urinary Incontinence and Comorbidities (EPIC) study, that recruited patients from Canada, Germany, Italy, Sweden, and the UK described that the prevalence of UI in women was of 13.1% [4]. The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study, carried in Sweden, the United States of America, and the UK estimated that UI in women ≥ 40 years was also highly prevalent. Despite not reporting a global prevalence of UI, they noted that stress UI affected 31.8% of the responders and urgency UI 24.4% [5]. In fact, SUI is the most prevalent subtype, affecting approximately 10% to 40% of women; while UUI, on the other hand, affects around 7% to 33% of women, both depending on risk factors and population groups. Although SUI appears as the most prevalent, followed by MUI and UUI, as women age this pattern tends to reverse [3,4].

While it can be assumed that Portugal presents similar epidemiological data, given that the aforementioned studies are mostly from western countries and that the pathophysiology of UI is the same regardless of the country, the reality is that available information remains scarce. One portuguese study from 2009, with 1483 women, reported a UI prevalence of 21.4%, with SUI being the most common type, present in 42.2% of individuals [6].

All these figures have public health implications, not only due to the direct health impact but also because of the associated costs and the unavoidable environmental impact. According to the 'An Urge to Act' manifesto by the European

Association of Urology (EAU), the economic burden of UI in 2023 was initially estimated at €40 billion being later revised to €69.2 billion across all European Union (EU) countries. A socio-economic report described by the EAU outlines the impact of UI in the EU from 2023 to 2030, including prevalence rates, healthcare costs, and environmental impact. These costs encompass not only the effects on individual health but also expenses related to medical consultations, continence products (which account for about one-third of the total costs), absenteeism from work (with productivity losses making up around 35% of the costs), nursing home admissions, and the environmental impact of managing incontinence. The economic burden for women is estimated to be four times higher than for men, and when factoring in the informal support provided by caregivers, the overall costs increase by 16%. The 'An Urge to Act' manifesto estimates that if no measures are taken to address continence health, the economic burden could rise by 25% by 2030, reaching €86.7 billion. Early estimates suggested that the cumulative economic impact could amount to €320 billion by 2030, however it is now understood that a more realistic figure is €552.2 billion. As the risk of continence issues correlates strongly with conditions that worsen with age, it is expected that these problems will escalate, especially given the rapidly aging population across Europe [7,8].

As specific data for Portugal are not available, we should assume that the impact will be proportionally significant, especially considering that its economic scale is smaller compared to many other EU countries.

Despite its high prevalence, UI remains underdiagnosed and undertreated within the portuguese healthcare system. Many women do not seek medical assistance due to stigma and a lack of awareness about available treatment options [6]. This exacerbates the public health challenge even further.

To face this challenge better education, prevention, and resource-wise management and treatment are fundamental. To address it, EAU launched another manifesto for policy reform on transforming EU Continence Health, based on the premise that policies and laws in EU countries often neglect continence care, despite its prevalence, gravity, and the availability of effective solutions. Endorsed by 23 organizations, the manifesto appeals for concrete policy changes, making

recommendations to European and national policymakers, emphasizing the importance of patient-centered continence care and promoting an understanding of the complex associations between continence health, healthy aging, women's health, and other comorbidities [8].

While public education, identifying risk factors, and prevention promotion, along with encouraging the role of caregivers—potentially reducing the need for nursing homes—can all benefit from the involvement of urologists, their role in these areas is not indispensable, as other professionals can contribute significantly as well. However, it is through offering more and improved treatments that the physician will have a pivotal and, above all, irreplaceable role.

Stress Urinary Incontinence

Regarding SUI, conservative management includes mainly lifestyle interventions and pelvic floor muscle training (PFMT) and should be the first line of treatment. Lifestyle interventions include diet, modulation of fluid intake, regulation of bowel habit, physical activity and weight loss. PFMT improves the function of the pelvic floor and should be offered supervised, as first line therapy, to all women for at least 3 months. When these measures are not successful, patients may wish to consider vaginal devices such as incontinence pessaries particularly if they want to avoid or are unfit for surgery [9,10].

If conservative treatment fails and the patients are candidates for surgery, the main operations for uncomplicated SUI are bulking agents, colposuspension, autologous fascial slings, and synthetic mid-urethral slings (MUS). In complex cases, such as women with a history of previous incontinence surgery, extensive pelvic surgeries, or even pelvic irradiation, external compression devices like adjustable compression therapy (ACT®), and especially artificial urinary sphincter (AUS), may be considered as treatment options [9,10].

Among all these options, MUS are probably the most extensively studied and the most frequently used surgical intervention in Europe for women with SUI [9]. They have become widely adopted due to their relatively low invasiveness, rapid execution, often in an outpatient setting, combined with sustained efficacy and an acceptable morbidity. Traditionally the retropubic and the transobturator routes of

insertion have been used, but more recently good evidence for the single-incision slings has emerged. Synthetic MUS inserted by the retropubic or transobturator route provide equivalent patient-reported outcomes at 1 year but the retropubic route has higher patient-reported cure rates in the long term, despite both having high satisfaction rates. They show a sustained response beyond 10 years. The retropubic route of insertion, compared with the transobturator route, is associated with a higher intraoperative risk of bladder perforation and a higher rate of voiding dysfunction. The transobturator route of insertion is associated with a higher risk of groin pain [9,11].

Single-incision or mini-slings offer the advantage of requiring only one incision with less tissue dissection, simplifying the procedure. This results in a shorter learning curve, making them easier for surgeons to master and thus more widely accessible to physicians, potentially increasing the number of women who could benefit from this option. Additionally, by avoiding extensive tunneling through anatomical structures such as the obturator foramen or retropubic space, mini-slings are associated with reduced morbidity, less postoperative pain, and shorter hospital stays [11,12]. Finally, although traditional MUS products have been proven safe and effective, they have not been exempt from the controversy surrounding mesh litigation related to pelvic organ prolapse repairs. Since the risk associated with mesh use is believed to increase with its surface area, mini-slings can in theory provide a favorable alternative, as they contain less synthetic material than traditional MUS [13]. However, some experts, based on their experience, suggest that the tension of single-incision slings needs to be adjusted tighter compared to the classic retropubic or transobturator MUS to achieve comparable outcomes [11].

The efficacy of mini-slings has been debated since their introduction, despite numerous studies being published. Due to significant variations in the technical design of different devices (some of which have already been withdrawn from the market), most studies cannot effectively aggregate mini-slings into a single category, raising concerns about drawing general conclusions regarding their performance. Moreover, many of these studies are short-term and lack the same level of quality seen in research on standard MUS [11,12]. Recently, a randomized controlled trial compared the efficacy of the Altis® and Ajust® single-incision slings

with conventional MUS. The findings indicated that single-incision mini-slings were non-inferior to standard MUS in terms of patient-reported success at 15 months, with similar success rates between the two groups at the 36-month follow-up. However, the rate of mesh exposure, repeat SUI surgery, and dyspareunia at the 3-year mark was higher for single-incision slings (Ajust® and Altis®) compared to conventional MUS [14]. Notwithstanding, there is still a lack of long-term data, and women considering single-incision slings should be informed that the long-term efficacy of these devices remains uncertain [12].

Urgency Urinary Incontinence

The therapeutic challenges of UUI are different from those concerning SUI. It is important to note that initial treatment may also benefit from lifestyle interventions (such as potential weight loss, fluid intake modification, reduced caffeine consumption), although these measures tend to have a greater impact on storage symptoms like urgency and frequency rather than UUI itself. Additionally, managing the patient's comorbidities and related medications can play a significant role, especially if the introduction of certain drugs has been associated with the development or worsening of urinary symptoms. These interventions are typically initiated alongside bladder training programs, although the optimal way to implement such programs is not well established. Alternatively, in older patients with cognitive impairments and those who are care-dependent, prompted voiding can improve incontinence. Concerning PFMT, included in first line interventions as well, the evidence is not clear regarding its benefit in UUI, being certainly lower than in SUI [12,15].

Pharmacotherapy is considered second-line treatment for UUI. However, in clinical practice, these medications are often introduced simultaneously with first-line measures. Anticholinergic drugs remain the cornerstone of treatment for UUI, although β3 adrenergic agonists are gaining predilection due to the low incidence of adverse events associated with its administration [16]. If anticholinergics fail to produce the desired effect, options include dose escalation, switching to another antimuscarinic, transitioning to a β3 adrenergic agonist, or even combining different drug classes. They are contra-indicated in case of narrow-angle glaucoma and in

patients using solid oral forms of potassium chloride, as the reduced gastric emptying potentially caused by the antimuscarinics may increase the potassium absorption of these agents. However, the real challenge with these pharmacological agents lies in their side effects: some, like xerostomia and constipation, often lead to discontinuation; while others, such as loss of memory and mental impairment, pose significant risks in long term use. Discontinuation is sometimes driven by unrealistic expectations, as patients may assume a rapid and complete return to their pre-symptom state. Additionally, many do not initially understand that UUI is a long-term problem requiring chronic medication, often leading to frustration when symptoms return after stopping the treatment [9,12,17, 18].

Regarding cognitive function, memory impairment and the risk of dementia are especially of concern in elderly patients who may already be vulnerable. An exception to this is trospium chloride, which does not cross the normal blood-brain barrier and therefore lacks the same potential for harm in most patients. Most other anticholinergics have studies showing no evidence of cognitive decline, but these are typically limited to 12 weeks of duration, which is insufficient for proper long-term assessment, since the effect is cumulative and increases with length of exposure [12]. A recent metanalysis with anticholinergic drugs used in overactive bladder syndrome (OAB) management concluded that anticholinergic use for ≥3 months was associated with a 46% increased risk of developing dementia [19]. Moreover, the anticholinergic burden may be a significative problem with the common polypharmacy seen in elderly patients. It is important to note that beyond cognitive decline itself, this loss of mental faculties often leads to a loss of independence, which studies have shown can increase the likelihood of requiring nursing home care, raising costs for both individuals and healthcare systems. On the other hand, discontinuation of antimuscarinics due to cognitive side effects can leave urinary symptoms untreated, further worsening quality of life and increasing care needs [20,21]. In contrast, the β3 agonists mirabegron and vibegron (the latter not available in Europe) belong to a different drug class and have adverse event rates similar to those of a placebo [12]. They are considered cognitively safe, even for elderly patients, although only mirabegron has phase IV studies [22,23].

Third-line treatments can be beneficial both due to the inefficacy of previous options or intolerance to side effects. These typically include invasive treatments such as tibial and sacral neuromodulation, and bladder injections of botulinum toxin [12,17].

Posterior tibial nerve stimulation (PTNS) delivers electrical stimuli to the sacral micturition center via the S2–S4 nerve roots. It can be administered using a percutaneous needle, inserted just above the medial aspect of the ankle (P-PTNS), or through transcutaneous surface electrodes that do not penetrate the skin (T-PTNS). Although PTNS is traditionally considered a third-line treatment, it is less invasive than other options (and T-PTNS is non-invasive), leading some to argue that it should precede or be used alongside drug therapy. The optimal treatment regimen is still uncertain, with both daily and weekly protocols described. However, even with weekly sessions, the burden associated with the 12-week induction phase followed by a maintenance program (for continued benefit a weekly stimulation would have to continue) may limit real-world adherence to treatment. Adverse events are relatively uncommon and mild. To address the limitations of PTNS, an implantable tibial nerve stimulator has been developed, but studies providing a direct comparison to other treatment modalities or placebo are still lacking, and therefore a recommendation specific to these implantable systems cannot be yet provided [12,17,18].

Sacral neuromodulation (SNM) involves implanting a battery device in the buttock and placing electrodes adjacent to the sacral nerve roots to deliver an electric current, specifically targeting the S3 sacral nerve root, thereby modulating neural activity. Although the exact mechanism remains only partially understood, this low-amplitude stimulation helps stabilize bladder function. Typically, patients first undergo test stimulation with either a temporary or permanent electrode to evaluate their response before moving forward with the permanent stimulator implantation. Currently, the only reliable predictor of treatment success with SNM is the patient's response during the test stimulation phase. Some drawbacks of sacral neuromodulation include a high adverse events rate, many leading to revision, such as unwanted changes in stimulation, lead migration, pain, infection or lack of efficacy. Patients should be informed that the device requires periodic replacement

(up to 15 years with the latest devices) in a planned surgical procedure and also must be willing to comply with the treatment protocol because treatment effects typically are only sustained as long as the therapy is maintained and have the cognitive capacity to use the remote control to optimize device function [12,17,18].

Concerning, bladder injection of botulinum toxin, the botulinum toxin approved in Europe for the treatment of UUI is onabotulinumtoxinA (onabotA; Botox®, Allergan, Inc., Irvine, CA, USA) at a dose of 100 U. Other subtypes of botulinum toxin, doses or formulations of botulinum toxin A (such as abobotulinumtoxin A and incobotulinumtoxin A) are not licensed for use in UUI. Moreover, the dosages for onabotA are not interchangeable with other brands of botulinum toxin A [12,24]. The lack of large studies with abobotA or incobotA for OAB treatment make the doses of these subtypes for UUI treatment unsettled. Botulinum toxin A acts by preventing acetylcholine release from nerve terminals, temporarily preventing involuntary detrusor contractions responsible for UUI. Additionally, an effect on sensory fibers was also demonstrated. The most common adverse effects following injection with 100U were urinary tract infection (UTI), incomplete bladder emptying requiring clean intermittent catheterization (CIC), and gross hematuria. The patient should be given appropriate counseling regarding the adverse effects as well as the long-term need for repeat injections (typically every 3-12 months) to maintain efficacy [12,17,18].

Clinicians may offer the third-line treatments in any order and may offer the alternate third-line treatment if a patient is refractory to the initial treatment choice. Therefore, it currently depends on multiple factors including patient preference, surgical expertise, available resources, and financial considerations. Despite this flexibility, some argue that SNM may be used as a “fourth-line” treatment option after failed treatment with botulinum toxin, not only because it is less invasive, but also because SNM may rescue some patients refractory to bladder injections [18,25].

In rare cases, the symptoms of UUI may be severe enough to justify consideration of fourth line therapies, such as augmentation cystoplasty or urinary diversion. The impact of these symptoms on the patient’s quality of life must be carefully weighed against the risks associated with major surgery, as well as alternative management

options, such as containment strategies (pads or diapers) [12,17,18]. Treatment selection, including the decision not to proceed with further therapy, depends on patient preferences, following a thorough discussion of benefits and disadvantages of each.

Given the diagnostic and therapeutic nuances, along with the specific profile of each patient and the potential economic and quality-of-life impacts, it is crucial to provide the most thorough characterization possible of these patients and the long-term options we can offer them. The present thesis commits to add evidence to some of these uncertain domains.

AIMS AND OBJECTIVES

Aim 1. Characterize the Portuguese reality with regard to female urinary incontinence

CHAPTER 1

Research Question 1. What is the prevalence of female urinary incontinence in Portugal and what do we know about socio-demographic data of these population, associated comorbidities and their impact on healthcare resources?

Aim 2. Assessment of the long-term treatment of female stress urinary incontinence

CHAPTER 2

Research Question 2. In patients with SUI, are mini-slings effective in the long-term?

Aim 3. Assessment of the long-term treatment of female urgency urinary incontinence

CHAPTER 3

Research Question 3. In patients with UUI, how good is botulinum toxin as long-term strategy of management?

CHAPTER 1

SELF-REPORTED URINARY INCONTINENCE IN WOMEN IS HIGHER WITH INCREASED AGE, LOWER EDUCATIONAL LEVEL, LOWER INCOME, NUMBER OF COMORBIDITIES AND IMPAIRMENT OF MENTAL HEALTH. RESULTS OF A LARGE, POPULATION-BASED, NATIONAL SURVEY IN PORTUGAL

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ORIGINAL ARTICLE

Self-reported urinary incontinence in women is higher with increased age, lower educational level, lower income, number of comorbidities, and impairment of mental health. Results of a large, population-based, national survey in Portugal

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Abstract

Purpose Urinary incontinence (UI) is a common condition in women. The aim of this study is to analyze women with self-reported UI, focusing on socio-demographic data, health-related conditions and comorbidities, and their impact on healthcare resources.

Methods We analyzed data from a population-based survey with a representative sample of Portuguese women aged ≥ 18 years ($n = 10{,}465$). Women with self-reported symptoms of UI were distributed according to age, education level, and household income. The comparison of comorbidities and use of healthcare resources between the UI and non-UI groups was adjusted for age, education, and body mass index. We computed weighted prevalence and adjusted prevalence ratios with 95% confidence intervals using Poisson regression.

Results Female UI prevalence was 9.9%, increasing with age (6.3% for 18- to 39-year-old, 40.8% for 75- to 85-year-old women). The prevalence decreased with education level (36.8% in women with no education, 4.6% in women with more than 12 years of education) and household income (29.8% in the 2nd quintile of income, 9.9% in the 5th quintile). Women with UI had a higher level of comorbidities, especially cardiovascular, respiratory, and mental health disorders. UI was also associated with higher consumption of healthcare resources.

Conclusion UI is highly prevalent among Portuguese women. It increases with age, low education level, and low household income. The use of healthcare resources was higher, possibly related with associated comorbidities. Though obtained in a single European country, these data may be useful to design a comprehensive management of UI in other parts of the western world.

Keywords Female urinary incontinence · Epidemiology · Mental health

Introduction

Urinary incontinence (UI), as defined by the International Continence Society (ICS) as the complaint of any involuntary leakage of urine, is a common disorder [1]. Different forms of UI are known, all affecting severely the patients' quality of life, and physical and mental well-being.

While lower urinary tract symptoms (LUTS) have similar prevalence in men and women, UI is more frequent in women [2, 3]. However, when we look at the studies reporting UI prevalence, the range of values presented across different countries is wide enough to raise questions concerning the etiology of those geographic asymmetries, since the known pathophysiological mechanisms are the same. The

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reported results are not adjusted to factors such body mass index, income, or education, and this may be one of the reasons for such observed differences.

Nevertheless, the burden of UI goes far beyond its frequency. It is difficult to separate health impact from social effect. Studies indicate that incontinence is associated with stress and depression. But also, the embarrassment and decreased ability to participate in social activities may lead to social isolation, which may further erode their overall mental health. The same reports link UI with deterioration in sexual life, and as women may be reluctant to discuss their condition with their partner, UI can strain personal relationships [4–7]. Finally, women with UI may face some challenges in their workplaces, with different repercussions according to their jobs. The concern with potential odors and the frequent toilet breaks may result in decreased productivity and even absenteeism.

This loss of productivity is interrelated with the economic impact of UI, being one of their major components. The economic burden is also felt in the healthcare costs, both at an individual level and to the healthcare system. All the expenses with consultations, diagnostic exams, and different treatments (medications, physical therapy, surgery, pads, and diapers) can be significant in a condition that may be chronic. As this paper is being written, European Association of Urology is sending to their associates a press release claiming that UI costs European society over 40 billion euros per year in 2023, including all the aforementioned reasons and also the environmental impact of incontinence care. They estimate a total accumulated economic burden of 320 billion euros in 2030, if nothing is done otherwise in an aging society.

Here, we aimed to expand the analysis of the impact of self-reported UI regarding age, socio-demographic data, and comorbidities, and how these parameters influence quality of life and the use of healthcare resources.

Methods

The present analysis is based on data collected as part of the National Health Survey (NHS) 2014, which is a nationwide community-based cross-sectional study that evaluated a sample of the Portuguese population, obtained through multistage stratified and cluster sampling.

This survey was approved by ethics committee, and all subjects provided signed informed consent.

Population sampling and data collection

A sample of households was defined using data from the 2011 Population and Housing Census and was used as the sampling frame for household surveys conducted by the INE. It included 1183 primary sampling units (PSU), selected systematically within larger geographical strata, with a probability proportional to the number of households in each unit. A random sample of the households was then selected, and all persons 15 years of age or older living in these households at the date of the recruitment were eligible. In each household, the selected individual was the one whose previous birthday was closest to the date of the contact. The sample size was defined to ensure a homogeneous distribution of the participants by the nine Territorial Nomenclature Units for Statistical Purposes, level II (NUTS II) regions.

Between September and December 2014, a total of 22 538 households were contacted, and 18 204 persons (56.4% women) were evaluated. Data were collected using either computer-assisted personal interviewing or computer-assisted web interviewing (50% in each regional stratum). The questionnaire covered four thematic areas: health status, healthcare, health determinants, and income and health expenses.

The diagnosis of urinary incontinence was assessed in the section of chronic diseases, answering the question "Have you suffered from urinary incontinence or bladder control problems in the last 12 months?".

A detailed description of the assessment of the participants' associated comorbidities, mental health status, and healthcare consumption is presented.

Statistical analysis

Data analysis was restricted to women aged ≥ 18 years that provided information on urinary incontinence, corresponding to a sample of 10,465 respondents.

We computed prevalence of urinary incontinence and used Poisson regression models to compute age- and education-adjusted prevalence ratios (PR) and respective 95% confidence intervals (95%CI) to compare women with and without urinary incontinence. All analyses were conducted with STATA, version 11.2 (StataCorp LP, College Station, Texas, USA), using sampling weights computed based on the design weight, that is, the inverse of the probability of selection of each PSU and of each household within each PSU, further corrected for non-responses and for the effective number of subjects evaluated, regarding the age and gender structures.

Results

The nationwide prevalence of female self-reported UI was 9.9% (95%CI 9.1–10.8%). UI increased with age, from 2.0% (1.1–2.9%) for the 18- to 39-year-old age stratum to 28.9% (25.6–32.2%) for the 75- to 85-year-old

women. The prevalence decreased with education level [28.2% (24.8–31.6%) to women with no education to 2.2% (1.2–3.2%) to women with more than 12 years of education]. Female UI prevalence also decreased with household income, ranging from 14.4% (12.3–16.4%) in the 2nd quintile of income to 5.3% (3.8–6.8%) in the 5th quintile.

Comorbidities

Women with UI had a high prevalence of comorbidities, especially hypertension [prevalence = 63.3% (95%CI: 59.0–67.5%)], obesity [27.8% (24.0–31.6%)], and diabetes mellitus [25.8% (22.0–29.7%)]. The age-, education-, and obesity-adjusted comparison between women with UI and those without UI demonstrated a higher level of respiratory [20% versus 8.6%, PR = 1.65 (95%CI 1.33–2.06)] and cardiovascular [24.8% versus 6%, PR = 1.69 (1.39–2.06)] diseases, and diabetes [25.8% versus 7.8%, PR = 1.40 (1.16–1.69)] (Fig. 1).

Mental health

The estimated prevalence of depression among women with UI was 36.9%, being approximately 66% higher than the prevalence observed among women without UI, with depression in 15.6% of the cases [PR = 1.66 (1.43–1.92)]. Regarding the mental health assessment, the survey also identified a higher prevalence of self-perceived health status as bad [47.8% versus 13.5%, PR = 1.65 (1.46–1.88)], difficulty in concentrating [41.2% versus 20.7%, PR = 1.58 (1.381.82)], and a feeling of worthlessness or guilt during the last 2 weeks [48.6% versus 25.4%, PR = 1.49 (1.33–1.67)]. There were no statistically significant differences between the two groups regarding addictive behaviors (Fig. 2).

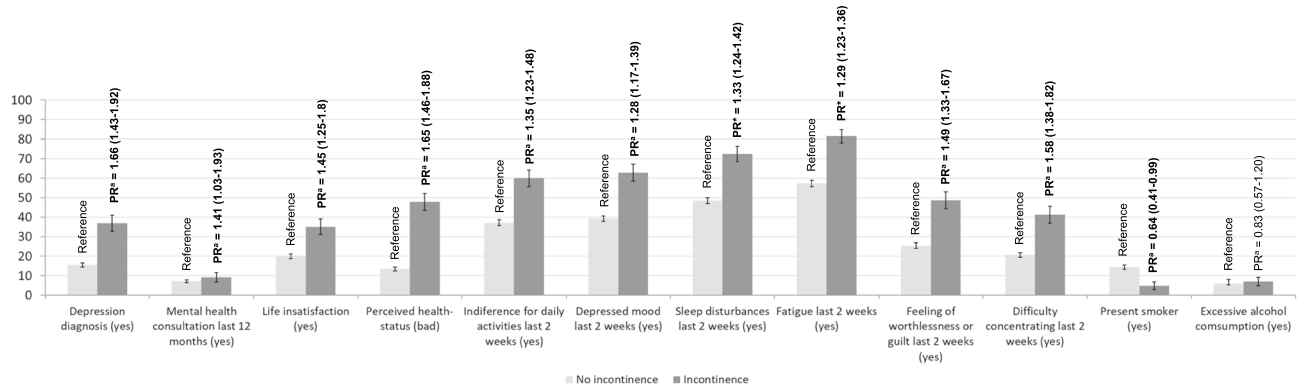

Fig. 1 Comparison of the prevalence of depression diagnosis, use of mental health consultations, different dimensions of mental health disease and addictive behaviours between UI women and non-UI women. **a** Age-, education-, and BMI-adjusted prevalence ratio and corresponding 95% confidence interval: PR (95%CI)

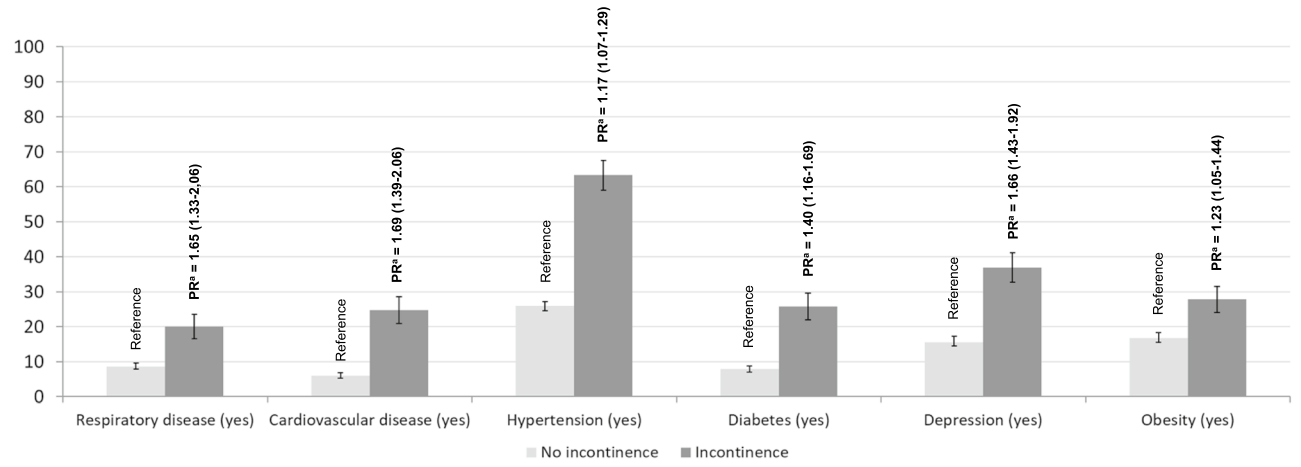

Fig. 2 Comparison of comorbidities between women with no urinary incontinence and urinary incontinence. **a** Age-, education-, and BMI-adjusted prevalence ratio and corresponding 95% confidence interval: PR (95%CI)

Use of healthcare resources

Female UI was associated with higher healthcare consumption, not only mental health evaluations [PR = 1.46 (1.06–2.00)] but also medical consultations in general [PR = 1.29 (1.19–1.39)], as well as prescribed medication [PR = 1.09 (1.05–1.14)] (Fig. 3).

Discussion

Several studies report female UI prevalence, with most of them estimating a percentage between 25 and 45% [8]. The larger studies, with the higher number of participants, included patients from several countries. In 2003, a study with women from France, Germany, Spain, and the United Kingdom (UK) reported a 35% overall prevalence of self-reported involuntary loss of urine in the preceding 30 days [7]. The Epidemiology Urinary Incontinence and Comorbidities (EPIC) study, that recruited patients from Canada, Germany, Italy, Sweden, and the UK, described that the prevalence of UI in women was of 13.1% [2].

Further epidemiological analysis in this area, with the Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study, carried in Sweden, the United States of America, and the UK estimated that UI in women ≥ 40 years was also highly prevalent. In spite of not reporting a global prevalence of UI, they noted that stress UI affected 31.8% of the responders, urgency UI 24.4%, and post-micturition UI 14.9% [3].

Our findings are in line with these data, with a nationwide prevalence of female UI of 9.9%, increasing with age, from 2.0% for 18- to 39-year-old to 28.9% for 75- to 85-year-old women. The rising prevalence with age is also consistent with the literature.

Our study adds an important information to the overall and age-related prevalence of UI, by analyzing for the first time the frequency of UI in conjunction with the educational level of affected women [2, 3]. In our analysis, it was clear that the prevalence varied with education level. UI was reported by 28.2% of women with low education in contrast with 2.2% among women with more than 12 years of education. The prevalence of UI was also inversely related to the household income, ranging from 14.4% in the 2nd quintile of income to 5.3% in the 5th quintile. This is surprising as one could expect that higher education and higher household income would increase the self-diagnosis and general knowledge about incontinence problems. However, there are some possible explanations to these numbers, considering that educational level and income may be interconnected. Women with lower education may have less knowledge about health in general and pelvic health in particular, regarding risk factors for UI and corresponding preventive measures. They are less likely to engage in a healthy lifestyle, which is one of the reasons why lower income populations have nowadays higher prevalence of smoking and obesity, two known risk factors for UI. Additionally, there is often a trend toward smaller family sizes as income rises, making lower income population more prone to higher parity, which is another risk factor to UI. They could also be more prone to certain occupations, more physically demanding or with more inflexible access to bathroom facilities, that may further exacerbate the condition. Furthermore, women with lower income have sometimes limited access to healthcare services, including not only treatment of UI but also preventive care. It is worth noting that this is particularly

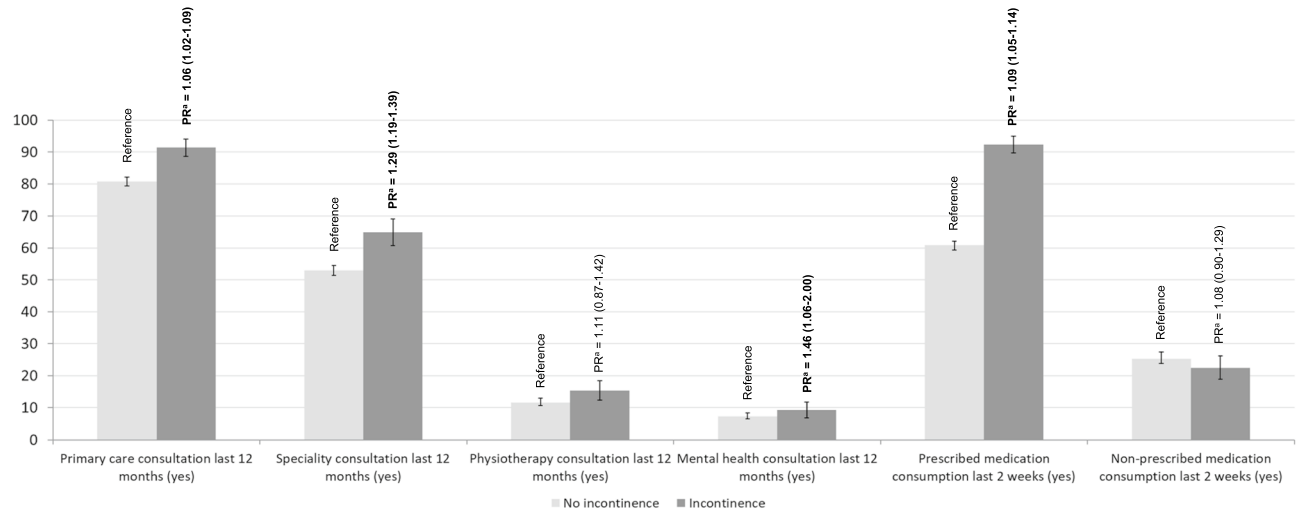

Fig. 3 Comparison of healthcare consumption between women with no urinary incontinence and urinary incontinence. **a** Age-, education-, and BMI-adjusted prevalence ratio and corresponding 95% confidence interval: PR (95%CI)

dramatic as this population with higher prevalence is precisely the one with more difficulties affording the costs of UI therapies and products.

We observed an association between women with UI and some comorbidities, such as cardiovascular and respiratory diseases. However, since this study applied a cross-sectional assessment, it is difficult to establish the causation link between the several comorbidities and the presence of female UI. Nevertheless, there are some possible justifications. Cardiovascular disease has a wide spectrum of manifestations. These patients have atherosclerosis and as a systemic disease it may have an impact in bladder arteries which, despite unproved, remains hypothesized as etiology to overactive bladder; they may have the need to take diuretics to control their hypertension or heart failure, or may simply be more prone to have obesity and diabetes as comorbidities. Regarding respiratory diseases, the presence of cough may increase awareness SUI. However, it may be also a consequence of attending more frequently medical facilities where women might be exposed to a better general medical care. By having more access to healthcare, it is possible that they become more aware that UI is a pathological condition and not a normal, integral part of aging, as sometimes patients unveil.

Regarding mental health domain, a subanalysis of the EpiLUTS study revealed that as the lower urinary tract symptoms increase, the outcomes in the questionnaires concerning quality of life, anxiety, and depression had worse outcomes [9]. Accordingly, the same survey showed that almost 50% of women with MUI and around 40% with UUI suffered from anxiety. In contrast, only 16.8% of women with pure SUI indicated some degree of depression [10]. Comparably, in our study, 60% of the women indicated a depressed mood, more than 1/3 had a diagnosis of depression and 10% were attending mental health consultations. Albeit there is not a proven cause effect link yet, incontinence undoubtedly affects mental health. The embarrassment caused by urine leakage in public places easily leads to isolation and depression. In this context urinary incontinence with an urgency component might be worse that pure stress incontinence due to its unpredictable characteristic. In addition, almost 50% perceived their health status as bad and reported a feeling of worthlessness. Interestingly, there were no relevant differences concerning addictive behaviors. Looking at this information, it is not surprising that incontinent women had higher healthcare consumption, including medical consultations, and received prescriptions.

In our view, what stands out of this evidence is that UI has a strong influence on women's well-being. Perhaps physicians should pay more attention to UI reported by women and actively investigate their UI status, offer a diagnostic work-up, research treatment, and refer the patients to a Urologist whenever necessary. Information of the community in general is also a fundamental step in our society, where many times, for cultural reasons leakage of urine is seen as a normal event in the aging process of women and therefore not always reported spontaneously to the doctors.

Our findings, coming from a large population-based study in Portugal, can most probably apply to other western countries, and perhaps to other societies despite their different cultural norms, health perceptions, and access to healthcare. It is important to stress that despite being more prevalent among women from lower educational level and lower income population, UI affect women across all socioeconomic backgrounds. Public health initiatives to promote health education and increase access to early intervention may reduce socioeconomic disparities, diminish healthcare economic burden, and improve patients' quality of life [11].

Conclusion

Urinary incontinence is highly prevalent in women, and it increases with age, low educational level, and low household income. Respiratory, cardiovascular, and mental health disorders are important independent comorbidities associated to female UI. The use of healthcare resources was also more prevalent among these women. Public health policies may mitigate this problem by raising awareness both in the population and in the clinicians. Education might prevent some cases by promoting healthier lifestyles and help reduce the impact of other cases by encouraging them to seek earlier treatment. A comprehensive approach to the condition is crucial.

Author contributions Margarida Manso contributed to data analysis and manuscript writing. Francisco Botelho performed data analysis. Cláudia Bulhões was responsible for project development and data collection. Francisco Cruz wrote the manuscript. Luís Pacheco-Figueiredo was involved in project development and data analysis.

Declarations

Conflict of interest The authors have no conflicts of interest to disclose. There is no funding to declare.

Ethics and Informed consent This survey was approved by ethics committee, and all subjects provided signed informed consent.

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CHAPTER 2

MINI-SLINGS: DO THEY STAND THE TEST OF TIME? A 10-YEAR COHORT

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Mini-Slings: Do They Stand the Test of Time? A 10-Year Cohort

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Keywords
Stress urinary incontinence · Single-incision slings · Mini-slings

Abstract
Introduction: It is known that failures after midurethral slings increase with the follow-up time. Nevertheless, data concerning mini-slings are sparse. To clarify this statement, we analyze a mini-sling cohort with a median follow-up of 10 years. Although the brand used, MiniArc®, is no longer available, an identical device, Solyx™, can still be used, which makes the analysis of the cohort clinically relevant. ***Material and Methods:*** A total of 172 women with predominant stress urinary incontinence (SUI) were consecutively treated with the mini-sling MiniArc® from 2006 until 2013. They were re-evaluated in 2018. The primary outcome, treatment success, was defined as no self-reported SUI symptoms and no reintervention. Secondary outcomes included the response to patient-reported outcomes. Adverse events were assessed. ***Results:*** After a median follow-up time of 113 months, 115 (66.9%) women were available for reevaluation. Forty-four (38.3%) women self-reported SUI. Seventeen women had been reoperated, 14 (12.2%) due to the reappearance of SUI and 3 due to complications. Altogether, MiniArc® had an overall success rate of 47.0% at 10 years. Among those not reoperated, 63.3% stated that they were much better or very much better in Patient Global Impression of Improvement (PGI-I) and 71.4% affirmed that their continence problem was normal or mild in Patient Global Impression of Severity (PGI-S). Almost 85% would repeat the surgery. Reoperation due to complications was rare (2.6%). De novo urgency appeared in 30.6% of the patients and it was managed with anticholinergic drugs with favorable outcomes. ***Discussion/Conclusion:*** This report adds evidence to the long-term outcomes of mini-slings, confirming that they can cure or improve SUI and give patients high satisfaction rates, at the expense of low morbidity.

Introduction

Stress urinary incontinence (SUI) is defined as the complaint of involuntary leakage of urine from the urethra, synchronous with exertion, sneezing, or coughing [1]. Despite varying according different populations, SUI overall prevalence ranges from 10 to 25%, making even

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more relevant the scrutiny of its methods of treatment [2].

When conservative management fails, surgery is the preferred option, with midurethral slings (MUS) being the recommended procedure to uncomplicated SUI [3]. First and second generation MUS, inserted either by retropubic or transobturator approach, have been proven to be effective and equivalent [4, 5]. However, the associated complications, as risk of bladder injury during retropubic approach and groin or thigh pain following transobturator route, led to the development of a third generation of MUS, the single-incision slings or mini-slings.

In the long-term, it is known that failures after SUI surgery increase with the follow-up time [6]. This fundamental analysis has been challenged in the case of the mini-slings by the different design of the tapes, some of which have very specific methods of insertion and fixation, making generalizations potentially incorrect. Nevertheless, at short-term follow-up, up to 2 years, standard MUS and mini-slings, TVTSecur® excluded, provide similar cure rates according to several meta-analysis [7–9]. A recent randomized controlled trial revealed an objective cure rate of 89% in the mini-sling group (MiniArc®), comparable to the 87% in the MUS group at 3 years [10]. Data with longer follow-up are very sparse, with few analyses suggesting a sustained efficacy of MiniArc®, 4–5 years after implantation [11, 12]. Therefore, the European Association of Urology (EAU) guidelines of 2019 maintain a strong statement that patients should be informed that the long-term efficacy of mini-slings remains uncertain, essentially similar to the one produced in the 2012 version [3]. To clarify this statement, data from cohorts with long follow-up time are relevant. Here we analyze a mini-sling cohort, MiniArc®, with a median follow-up of 10 years. Although MiniArc® brand was discontinued, a similar device is available under the trade name of Solyx™, which makes the analysis of the cohort relevant.

Materials and Methods

A total of 172 women with predominant SUI were consecutively treated with the mini-sling MiniArc® (American Medical Systems, Minnetonka, MN, USA) from 2006 until 2013 at a tertiary center. Although no longer available with this name, a tape with the same anchoring structure and similar mesh material of MiniArc® is still accessible as the Solyx™ mini-sling (Boston Scientific Corp., Natick, MA, USA). From the 172 women treated with MiniArc®, 115 (66.9%) were available for reevaluation.

The primary outcome for this study was the success rate defined as no self-reported SUI symptoms and no reintervention for SUI or sling removal due to complications. Secondary outcomes included the response to patient-reported outcomes: Patient Global Impression of Improvement (PGI-I) and Patient Global Impression of Severity (PGI-S) questionnaires, and the question "would you repeat the surgery" [13]. Adverse events were also evaluated. For statistical analysis we used SPSS® software, version 25.0.

Results

A total of 115 women from the initial population were available to determine the success rate of the mini-slings, 66.9% of the total MiniArc® patients. Lost patients either had deceased or were no longer available in the contacts available in the hospital. The patients were evaluated between May and July 2018 with a median follow-up of 113 months. The mean age of women at the time of surgery was 52 ± 11 years.

When inquired about symptoms of SUI, 44 (38.3%) women self-reported SUI. Seventeen women had been reoperated, 14 (12.2%) due to the reappearance of SUI and 3 due to complications. This led to a success of MiniArc® at 10 years in 54 women making an overall success rate of 47.0%. Figure 1 summarizes patients' distribution.

Among those not reoperated (98 women) in the PGI-I, 63.3% stated that they were much better or very much better. In 17.4%, some improvement was still found. Only 3% declared they were much worse or very much worse (Fig. 2). In the PGI-S, the continence problem was normal or mild in 71.4% of the patients, while only 8.2% reported that the situation was severe (Fig. 3). When asked "would you repeat the surgery," 83.7% answered affirmatively.

Reoperation due to complications was rare (2.6%). Acute urinary retention led to cut the MiniArc® tape in 2 women, and in one the MiniArc® was removed due to vaginal exposure/erosion. Ten out of the 17 women reoperated due to reappearance of SUI or complications had the second surgery within the first 24 months after the mini-sling placement, in the majority of the cases with a standard MUS. De novo urgency appeared in 30.6% of the patients and it was managed with anticholinergic drugs with favorable outcomes.

There were no differences in all these parameters when patients with less or more than 113 months of follow-up were compared.

Discussion/Conclusion

The long-term efficacy between standard MUS and mini-slings has remained a non-solved issue in the last editions of EAU guidelines. The most recent meta-analy-

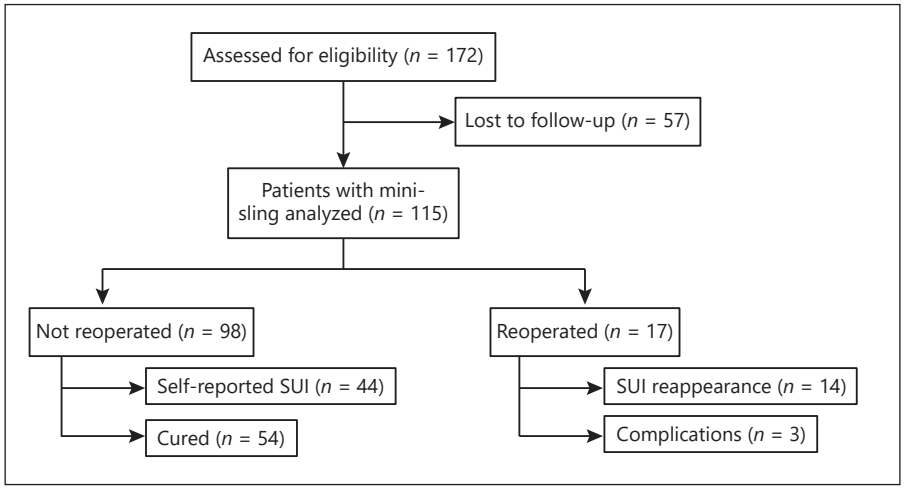

Fig. 1. Patients' distribution. SUI, stress urinary incontinence.

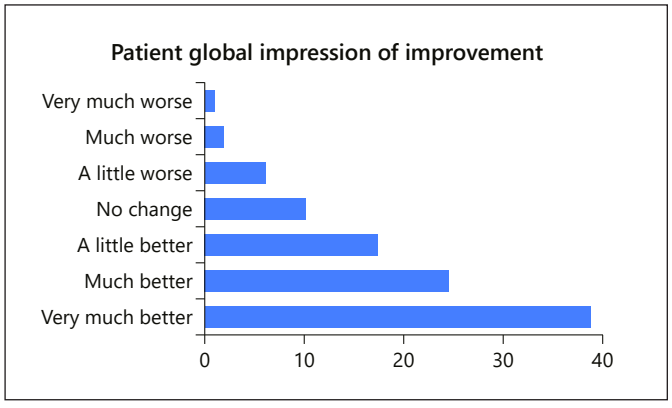

Fig. 2. PGI-I. PGI-I, Patient Global Impression of Improvement.

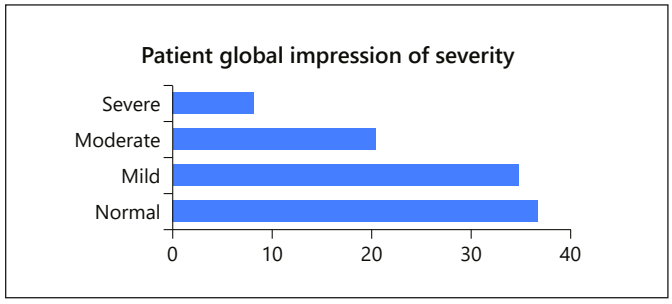

Fig. 3. PGI-S. PGI-S, Patient Global Impression of Severity.

sis with an average follow-up of 2 years concludes that objective cure rates were inferior in mini-slings, emphasizing, however, the similar outcomes between the 2 types of tapes when subjective cure rates were compared [14, 15].

Regarding overall objective cure rate, after 10 years, 47.0% of our population was dry. These results are very similar from those of the TOMUS trial for MUS at 5 years (retropubic with 51.3% and transobturator with 43.4% of success), which used the same outcome measures for success [6]. They were adopted at the design of the study in order to make comparisons more trustworthy.

Subjective cure rates, measured through patient-reported outcomes, are becoming increasingly relevant in clinical trials since patient perception of cure is the ultimate purpose of incontinence surgery. In the MiniArc® cohort, after 10 years of median follow-up, 71.4% of the women that had no reoperation stated their continence problem was normal or mild in PGI-S and 63.3% stated that they were still much better or very much better in PGI-I. Furthermore, >80% of our patients would repeat the surgery knowing the current results.

According to the TOMUS trial, notwithstanding with its decreased efficacy over time, the satisfaction rates at 5 years also remained high with MUS (retropubic with 79% and transobturator with 85%) [6]. Also, in a randomized clinical trial comparing MiniArc® and a MUS, the values in the PGI-I were identically high after 3 years for the mini-sling (86%) and MUS (87%) [10]. Altogether, these data demonstrates a high patient satisfaction at 10 years after the placement of MiniArc® and stresses the fact that eventual small losses, without significant interference in the quality of life, may also be perceived by patients as positive outcome.

Only 3 (2.6%) women had complications requiring intervention, highlighting the good safety profile of these devices. It was, actually, the need for a simpler procedure

(one small incision and a limited tissue dissection), with less postoperative complications (bladder perforation or inguinal pain), that motivated the single-incision sling development. In addition to its simpler technique, the mini-sling provides a device with less synthetic material in the body of women. In recent meta-analysis, mini-slings were associated with significantly shorter operation times, lower immediate postoperative pain, lower intraoperative blood loss, and lower postoperative voiding dysfunction [14, 15]. The amount of synthetic material may be increasingly important as more studies suggest that it is related with some of the potential complications including the mentioned inguinal pain and the negative effect on sexual function. That would explain why the improvement in sexual life is higher with mini-slings than with standard MUS, as stated in EAU guidelines [3].

The literature available for standard MUS after 10 years of follow-up disclosed much higher cure percentages after transobturator MUS insertion, of nearly 90% based on negative cough stress test, which may give higher rates than criteria based on no reoperation and no self-reported outcome measure here used [16]. However, for the same type of sling and similar follow-up time, other authors did not reproduce these results. The objective cure rate based on a negative cough stress test was 78.9% while the subjective one was only 62.6%, again highlighting that the cough stress test may show unexpected better outcome rates [17]. In another cohort with 10 years follow-up in which only retropubic MUS were used, the satisfaction rate was also of 62.6%, after a slow decline along the years [18]. The subjective assessment of the patients reported by these cohorts is, therefore, comparable with our rates of satisfaction in PGI questionnaires.

In this series, patients developed de novo urgency in 30.6%, a percentage that, although high, can be expected in a population followed-up 10 years. To the de novo urgency may concur not only the increase of overactive bladder symptoms after MUS placement but also the increasing incidence of such symptoms with aging [19]. It is, therefore, surprising that long-term studies regarding MUS do not reflect this incidence that is similar across the world [20–22]. A recent study reported de novo urgency in only 14.4% of their patients at 10 years after a retropubic MUS, despite the annual incidence of overactive bladder symptoms that, in the lowest range, overpasses 3% per year [18, 23]. Eventually, we cannot exclude that the placement of the mini-sling meshes, abutting the urethra, may increase de novo urgency, an aspect that should be object of investigation in the future.

This report adds evidence to the long-term outcomes of MiniArc® mini-sling, confirming their capacity to cure or improve SUI and give patients high satisfaction rates, at the expenses of a low morbidity. The latter aspect is particularly relevant because the Solyx™ device has a similar anchoring system and same mesh material. Moreover, the small amount of artificial mesh that is used in a MiniArc®-like mini-sling may further increase the safety of the procedure. In fact, in a recent consensus meeting the amount of artificial mesh used in the treatment of pelvic organ prolapse was recognized by all experts as a main reason for the severe complications reported worldwide [24]. Similar complications have not been reported after placement of MUS, which use smaller amounts of mesh. Using the same rationale, the probability of such dreadful events after a mini-sling, which were not seen in our patients, should be even less likely. Moreover, if their cost-effectiveness is contemplated, it stands no question that this surgical approach should be considered as potential superior to standard MUS. Eventually the possibility of performing the mini-sling surgery as an ambulatory procedure and under local anesthesia may contribute for that and may contribute to decreasing the costs associated with the treatment of SUI [15, 25].

As strength of this study we should highlight the fact that we considered cure as a strict objective measure, while most trials measure subjective outcomes, contemplating both cure and improvement, with consequent higher success rates. There are some limitations of this study though: it is a single center study and the overall information includes a device already withdrawn from the market, MiniArc®, despite the fact that Solyx™ is similar in what concerns the design of the anchoring system and the type of mesh used. Mini-slings might be offered to women seeking long-term cure of SUI through a minor surgery virtually free of severe complications, as cure of SUI and a high degree of satisfaction were reported by almost 50% and by >75% of women 10 years after the procedure, respectively.

Statement of Ethics

Subjects treated with single-incision slings have given their written informed consent, and the study protocol was approved by the Ethics Committee of the institution in 2010, when a short-term prospective study was conducted. To perform this long-term retrospective analysis, no written consent was obtained, in line with the policies of the institution.

Conflict of Interest Statement

Francisco Cruz has been a consultant to Boston Scientific. The other authors have no conflict of interests.

Author Contributions

Margarida Manso: data collection and manuscript writing; Francisco Botelho: data analysis; Carlos Silva: data collection and project development; Francisco Cruz: data analysis and manuscript writing.

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CHAPTER 3

EFFICACY, SATISFACTION AND COMPLIANCE: INSIGHTS FROM 15 YEARS OF BOTULINUM TOXIN USE FOR FEMALE URGENCY URINARY INCONTINENCE

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Efficacy, Satisfaction, and Compliance: Insights from 15 Years of Botulinum Toxin Use for Female Urgency Urinary Incontinence

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Abstract: Urgency urinary incontinence (UUI) refractory to medical treatment poses significant challenges despite advancements. This study evaluates the efficacy of intravesical botulinum toxin for UUI and identifies factors influencing treatment outcomes. Among 368 women receiving botulinum toxin injections, 74.5% achieved a complete discontinuation of pad usage. Predictors of efficacy included lower pre-treatment pad usage and the absence of prior sling placement. Patients often required repeat injections (60.3%), with younger age and satisfaction correlating with treatment repetition. The interval between injections averaged 18 months, influenced by logistical challenges and patient preferences. Despite concerns about diminishing efficacy, subjective perceptions did not align with objective findings. Limitations include retrospective analysis and heterogeneous clinical records. In conclusion, intravesical botulinum toxin is effective for UUI, with pre-treatment pad usage and sling placement history influencing outcomes and patient characteristics influencing treatment repetition.

Keywords: female urinary incontinence; urgency urinary incontinence; overactive bladder; bladder botulinum toxin; Botox®

Key Contribution: UUI treatment with botulinum toxin type A bladder injection maintains a long-term constant efficacy, and intervals between treatment cycles are wider than expected from pivotal trials. Patients with a more severe condition and a history of previous slings procedures should be informed about their lower likelihood of success.

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1. Introduction

While urgency urinary incontinence (UUI) may not be the most common form of incontinence, it often prompts individuals to seek medical attention more frequently than other types. Most cases are idiopathic, and it is generally assumed to be associated with the aging process, although other risk factors are identified [1,2].

According to European Association of Urology guidelines, the first-line treatment of UUI, whether included or not in the overactive bladder (OAB) syndrome, relies on lifestyle interventions and bladder training, with second-line being pharmacotherapy. Anticholinergics have revolutionized the treatment of UUI, but the associated side effects and the need for continuous medication lead many patients to discontinue treatment. Despite valuable additions such as beta-3 agonists, a substantial number of cases either do not improve or show only limited progress. When pharmacotherapy fails or cannot be tolerated, a bladder wall injection of botulinum toxin is one of the third-line therapies [2,3].

However, it is essential to acknowledge that even with this therapy, there are both refractory patients and individuals who, over the long term, discontinue treatment despite initially positive responses. The reasons for such discontinuation remain unclear and

cannot be determined by pivotal studies. Therefore, in this study, we aim to clarify if we can predict which patients will respond favorably or unfavorably, if there are factors influencing the efficacy and duration of the treatment, and which patients are more likely to request repeated injections, as well as the efficacy of botulinum toxin in treating UUI in real-life conditions.

2. Results

The study involved 368 women diagnosed with UUI between 2010 and the last quarter of 2023, all of whom underwent bladder injections of botulinum toxin. Patients injected after that date were not included due to the inability to properly analyze the duration of the treatment. Of the 368 patients analyzed, the mean age at diagnosis was 60.4 years (SD ± 14.1) and had an average BMI of 30.3 (SD ± 5.4). In this cohort, 27.7% had undergone a previous mid-urethral sling placement. Among those with available information, 67.7% had a transobturator tape, 25% had a single incision sling, and 7.3% had a retropubic sling.

Among the 306 patients with complete information concerning pad usage, the median number of pads used per day before botulinum toxin injection was 3 (p25–p75: 2–5), which subsequently decreased to 0 (p25–p75: 0–1) post injection. The majority (74.5%) of patients reported a complete discontinuation of pad usage after treatment, while 25.5% continued to use one or more pads. In this group are included 7.2% of patients who had no improvement.

In 60.3% of cases, additional injections were deemed necessary, with a median of 1 (p25–p75: 0–2) additional treatment (Table 1) and a median time until the second injection of 18 months (p25–p75: 11–29).

Table 1. Number of patients by number of treatments requested after the first procedure.

Number of Treatments	Number of Patients (%)
0	146 (39.7)
1	114 (30.9)
2	61 (16.6)
3	24 (6.5)
4	8 (2.2)
5	7 (1.9)
6	6 (1.6)
7	1 (0.3)
8	1 (0.3)

The number of pads used at baseline predicted the chance of being dry after botulinum toxin injection. As a matter of fact, it was observed that the lower the number of pads used before the treatment, the higher the likelihood of achieving a pad-free situation. Specifically, women who discontinued pads after onabotulinumtoxinA (onabotA) had an average of 3.5 pads pre-OnabotA while those who still required pads had an average of 4.8 pads pre-OnabotA ($p < 0.05$). Additionally, patients who had undergone sling placement were less likely to achieve continence. Among those without previous sling placement, 77.9% achieved pad-free status after OnabotA treatment compared with 65.8% among those with prior sling placement ($p < 0.05$). No statistically significant relationship was identified between BMI and the number of pads before and after injection.

Regarding the request for new treatments, women who repeated the injection at least twice were, on average, younger at the time of diagnosis (57.3 years, SD ± 16.1) compared to those who did not repeat injections (61.7 years, SD ± 13.1) ($p < 0.05$). Furthermore, patients who reported satisfaction were more likely to undergo repeated treatment than those who expressed dissatisfaction ($p < 0.05$).

In the multivariate analysis model, which included the variables age, BMI, previous slings, and the previous number of pads, only the previous number of pads was an independent predictor of having zero pads after injection (adjusted OR 1.12; $p = 0.042$).

The complications associated with the treatments were mild. There were 4 patients with urinary retention requiring temporary urethral catheterization (1.1%) and 29 (7.9%) with symptoms of urinary tract infection treated with oral antibiotics.

3. Discussion

Only onabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA, USA) 100U is licensed in Europe to treat UUI/OAB, and it is relevant to note that it is more effective in curing UUI than antimuscarinics, being a third-line treatment based on the assumption that intervention therapy should follow oral medication [2,3]. Sacral nerve stimulation is also a third-line treatment; however, so far, the trials demonstrated that the neuromodulation is comparable not with 100 U but with 200 U of the same toxin. Additionally, the increasing invasiveness, more serious complications, and higher costs of the two-stage implantation procedure should be mentioned, despite the potential need for just one (two, in fact) intervention [4,5]. However, that is beyond the scope of this paper.

The introduction of intravesical botulinum toxin treatment has been a significant advancement. It began to be used to treat medical conditions by the end of the 1970s, but it was only applied in urology in 1988, being used to treat urinary incontinence a few years later [6]. The first significant studies and clinical applications of botulinum toxin for treating UUI emerged around the early 2000s, and by 2009, substantial evidence supported its efficacy for this condition, leading to broader use in clinical practice. It is a neurotoxic protein produced by *Clostridium botulinum*, with seven subtypes. Subtype A has the longest duration of action, which makes it the most clinically relevant [2,6].

Botulinum toxin subtype A consists of a heavy and a light chain linked by a disulfide bond. When it is injected, it infiltrates the nerve terminals and enters the presynaptic neuron membrane through binding of the heavy chain to the synaptic vesicle protein (SV2). The heavy chain of the toxin exhibits an affinity for polygangliosides located on the surface of neuronal terminals, thereby augmenting the toxin's concentration on the neuronal membrane. This heightened concentration enhances the likelihood of the heavy chain encountering the protein acceptor SV2 predominantly expressed within synaptic vesicles. After toxin endocytosis, acidification within the synaptic vesicles precipitates the elimination of the disulfide bond and the dissociation of the two chains. The light chain protein, which is the true active part, is then linked to the synaptosomal nerve-associated protein 25 (SNAP-25). When the light chain links to SNAP-25, it cleaves it and inactivates it [2,6]. By cleaving SNAP-25, it hinders the proper formation of the SNARE (Soluble NSF Attachment Protein Receptor) complex. As the SNARE complex mediates the binding of neurotransmitters vesicles to the plasma membrane of the nerve terminals, so they can fuse and release acetylcholine (Ach), and, consequently, this prevents Ach exocytosis from the vesicles. Why is this Ach blockage so essential? Because if during the voiding phase it plays a crucial role in bladder contraction to facilitate urine evacuation, during the storage phase, its effect is undesirable since there is no physiological parasympathetic input to the lower urinary tract. However, ACh can be spontaneously released from nerves and non-neuronal structures, including the urothelium and suburothelium, during this phase. This release can activate afferent nerves innervating the bladder, potentially causing urgency and UUI. When the cascade of events due to botulin toxin bladder injection occurs, as Ach is not released, it cannot bind to muscarinic receptors on the bladder detrusor muscle, thereby averting undesired contractions [2,7,8]. Furthermore, adding to this motor/efferent modulation, botulinum toxin reduces the expression of sensory receptors in bladder nerves by hampering their transfer from intracellular vesicles to the neuronal membrane, also modulating the sensory/afferent component of the disease [9].

What sets different commercial forms apart is the molecular weight of the accessory protein that covers the toxin. Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany), Dysport® (Ipsen Biopharm Ltd., Wrexham, UK), and especially Botox® (Allergan, Inc., Irvine, CA, USA) are the best known. Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany) has a molecular weight of only 150 kDa, Dysport® (Ipsen Biopharm

Ltd., Wrexham, UK) around 400 kDa, and Botox® (Allergan, Inc., Irvine, CA, USA) 900 kDa. Consequently, posology, the potency per weight of each brand, is unique and not interchangeable [10]. This was the reason behind the FDA introducing the non-proprietary names of incobotulinumtoxinA (incobotA) for Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany), abobotulinumtoxinA (abobotA) for Dysport® (Ipsen Biopharm Ltd., Wrexham, UK), and, as previously mentioned, onabotulinumtoxinA (onabotA) for Botox® (Allergan, Inc., Irvine, CA, USA) [2].

Despite the dose depending on the chosen toxin brand, the preparation method is similar. It is important to note that during reconstitution, vials should be gently stirred rather than shaken, as vigorous agitation may disrupt the delicate disulfide bond linking the light and heavy chains of the botulinum toxin molecule [10]. Regarding its administration, it requires the injection of a toxin solution into the bladder wall, as the toxin fails to cross the urothelium upon instillation into the bladder. Efforts to facilitate this process have so far yielded limited success or await a definitive validation of efficacy. For patients with OAB undergoing a bladder injection of onabotA, the standard administration implies 20 injections of 0.5 mL each, classically sparing the trigone. However, despite these recommendations regarding the number of injection sites, many clinicians opt for a reduced number of injection points. Non-randomized controlled studies have utilized one or three injection sites, each receiving 1–5 mL of solution, in the posterior bladder wall, or alternatively, three to four injections of 2 mL each at the equatorial line of the bladder, with no apparent compromise in efficacy [11–13]. Investigations into injections in the trigone have been predicated on the premise that this region of the bladder harbors the highest density of sensory fibers. It is hypothesized that a combination of injections in the bladder walls and trigone may yield greater effectiveness than injections confined solely to the bladder walls in cases of OAB [14,15]. More recently, some studies explored further the reduced number of injections and a different location, offering reassurance that fewer injections seem equally effective, and that trigone inclusion could be as, or even more, effective, as targeting the lower bladder could reduce the urinary retention by maintaining upper bladder function [16–18]. The depth of injections, whether intradetrusor or suburothelial, has been the subject of a meta-analysis, which found no discernible differences in efficacy or safety. Large-scale clinical trials have not detected antibody formation following initial administration. However, to mitigate the risk of immunosensitization, a 12-week interval between injection cycles is recommended [9,10].

This treatment has successfully addressed a significant percentage of patients who did not respond to previous interventions, with effects lasting for an average of 6 months, according to pivotal trials [14,19]. The primary complications of intradetrusor injections of botulinum toxin A are urinary tract infections and urinary retention. Patients should be informed that they might require temporary (self-)catheterization. Yet, the treatment offers the advantage of virtually no systemic side effects [20].

As UI prevalence is high and its impact on women's lives is substantial, it is imperative to conduct a comprehensive examination of all facets related to its treatment to ensure the delivery of increasingly efficacious care [21,22]. Notwithstanding this, probably because its efficacy has already been established, recent studies analyzing it are scarce, especially in an idiopathic context and even more specifically in the female population. This scarcity is even more pronounced if we consider it from a patient-reported-outcomes perspective, or with apparently less objective measures such as the number of pads, which may actually be the best surrogates for a patient's quality of life. Furthermore, the latest evaluations available focus on urodynamic parameters. Notably, one of the key urodynamic markers for OAB is detrusor hyperactivity, which is not always necessary for diagnosis.

Therefore, when we say that the primary objective of this study is to assess the efficacy of botulinum toxin, we are addressing something directly applicable to real-life practice: this can inform a patient about the probability of no longer needing to use pads following the treatment. It is remarkable that 74.5% of patients reported a complete discontinuation of pad usage post treatment, but it is essential to acknowledge that this rate includes only

those achieving complete dryness, as there were women still employing pads but who experienced significant improvements, leading to great changes in their quality of life. As such, of the remaining 25.5% patients, some exhibited a positive response to Botox; and some, with a negative response in the first treatment, underwent a second treatment to address dosage and technical issues as potential causes of the initial failure.

As the main determinants of efficacy, we identified the number of pads used before treatment and a history of sling placement, both exerting influence on treatment outcomes. The former is inherently predictable, given the association between the severity of UI and treatment challenges. Furthermore, certain patients not responsive to conservative management, due to antimuscarinic intolerance, may signify a more easily treatable condition, correlating with a higher success rate [23]. However, the latter finding deviates from prior reports demonstrating similar efficacy in women with or without a history of previous sling surgery [24]. In the present investigation, there appears to be a trend towards a less favorable clinical outcome in patients with a history of prior sling procedures. Despite timely reassessment for obstruction in patients upon UUI development, one could argue that sling surgery often augments bladder outlet resistance, yielding functional consequences even in cases with low post-void residual and high flow rates. Supporting this contention, urinary NGF, elevated in female rats with bladder outlet obstruction, was similarly elevated in reports of patients after sling placement, comparable to levels previously described in patients with overactive bladder [25]. Moreover, some studies suggest that increased bladder outlet resistance after a sling procedure may significantly contribute to the rise of urinary neurotrophins, promoting the sensitization of bladder primary afferents and inducing de novo urgency in susceptible patients [26]. This finding could prompt a new line of inquiry into whether patients with a sling truly have idiopathic UUI or if the sling itself was the cause. In both cases (high number of pads used before treatment and a history of sling placement), we should be more emphatic explaining to the patient the lower probability of success, as expectations are decisive in the therapeutic process. These will be the most challenging patients, but also the ones more in need for a solution.

Despite an average interval of approximately 6 months, pivotal trials indicate the need for repeat injections with intervals ranging from 3 months to over a year [27,28]. Patients received a second injection after a median duration of 18 months. Although surprisingly long, it is important to note that this interval does not necessarily equate to the duration of therapeutic effect. Over nearly 15 years, various factors contributed to this timeframe, albeit some no longer relevant today. Logistical challenges, including temporary follow-up losses and delayed post-Botox evaluations, contributed to this timeframe, with patients often waiting excessively to consult their urologist. Additionally, some patients were still pleased with the tail effect of the previous toxin injection, which means that, although lacking the full influence from the treatment, they were still satisfied, not seeking a new one. It is also noteworthy that some women opted to defer a second treatment even when the initial one was no longer effective, primarily due to the invasiveness of the procedure, carried out in the operating room under sedation, prompting a desire to avoid it.

This highlights the necessity of finding a novel method of botulinum toxin administration. To date, the administration requires the injection of a toxin solution in the bladder wall since the toxin does not traverse the urothelium if instilled in the bladder [29]. Various facilitators for enhancing the transurothelial passage of the toxin have been explored, including liposomes, the reverse thermal gelation TC-3 hydrogel, low-energy shock waves, and electromotive administration [30–33]. However, botulinum toxin encapsulated in liposomes did not produce results robust enough to pursue its development in OAB. It also failed when mixed in reverse thermal biodegradable hydrogel that increases viscosity at body temperature. Three thousand low-energy shock waves delivered during 10 min to the bladder half-filled with a solution containing 100U onabotA provided short-lasting effects. Electromotive administration has also been investigated without success. Facilitators for the passage of the toxin through the urothelium have so far failed or did not show irrefutable efficacy. The use of the needle in a flexible cystoscope, with a local anesthetic

agent such as lidocaine, may also allow to perform an in-office procedure, which is simpler for the patients to repeat [34].

This phenomenon is interconnected with the repetition of the procedure across the years. While age at diagnosis and satisfaction emerged as determinants for procedure repetition, certain patients, even those young and satisfied with the results, opted to postpone it even when already losing efficacy. We attribute it to the aforementioned reasons.

Although older patients of the cohort appeared to request fewer treatments, the issue of age prompts further reflection. While the safety of onabotulinumtoxinA administration in elderly patients has been established, the same is not entirely true for previous treatment lines such as anticholinergics. In fact, the chronic use of anticholinergic drugs is increasingly being challenged due to growing evidence that prolonged exposure may lead to cognitive deterioration, particularly among elderly patients already at risk of dementia [35]. Moreover, a systematic review has shown that botulinum toxin injections are significantly more effective in curing UUI compared to any form of oral medication [36]. Given these considerations, should intravesical botulinum toxin be contemplated or even prioritized before anticholinergics, in an aging population?

Another matter of concern is the loss of efficacy over time. While subjective patient perceptions in clinical practice suggest diminishing efficacy with subsequent injections, our findings did not corroborate this observation. Furthermore, studies indicate a reduction in urgency severity associated with long-term therapeutic effects, aligning with real-world practice observations [37].

The principal limitations of our results stem from the retrospective nature of the study and the heterogeneity of clinical records among urologists, including the absence of standardized questionnaires or bladder diaries, which complicates the objective quantification of patient improvement without introducing biases. There are several points where this could be more evident. First, as the number of pads used is not consistently reported in clinical practice, the magnitude of improvement with the injections is probably higher than indicated. Conversely, complications from the treatment are likely underreported, as some are resolved before patients contact their urologist or are not detailed in clinical records. Additionally, demographics such as BMI, which we did not find to correlate with outcomes, might have shown correlations if we had a larger dataset, as analyses from randomized studies showed that a higher BMI is associated with a decreased time to recurrence [38]. Finally, regarding patient selection, it is possible that relevant information from patient clinical history was not recorded, preventing us from excluding women with identified causes of UUI.

As we acknowledge that many of the limitations of this study are due to its retrospective nature, future research should ideally be conducted prospectively, with all research questions defined in advance. Women for whom the treatment is effective but still decide to discontinue are intriguing. Does the procedural context—typically performed in an operating room—play a significant role? Do they never return to their baseline status and feel good enough? These are questions that remain to be addressed.

4. Conclusions

Intravesical botulinum toxin is a highly effective treatment. A clear correlation exists between a lower pre-procedural pad usage and a higher likelihood of achieving continence. Contrarily, patients with a history of sling placement for stress urinary incontinence who developed UUI exhibited a reduced likelihood of attaining continence. Furthermore, younger women at the time of diagnosis demonstrated an increased inclination to seek repeated injections, a trend mirrored in patients expressing greater satisfaction with the initial procedure. Surprisingly, in real-life conditions, patients often delayed the next injection longer than anticipated.

5. Materials and Methods

This is a retrospective observational cohort study. Women over 18 years old with a diagnosis of UUI, included or not in the OAB syndrome, were included if they were refractory to conservative treatment. All eligible patients had not been adequately managed with one or more anticholinergics and/or b3-adrenergic receptor agonists for UUI treatment, due to insufficient efficacy or intolerable side effects. Patients underwent treatment with botulinum toxin injection between 2010 and 2023. Women with an identified cause for their clinical condition were excluded, as well as those whose first treatment was performed in the last quarter of 2023, as it was deemed insufficient time for a proper reassessment of the need for new injections.

OnabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA, USA) was the administered toxin in all patients. It was administered under light sedation using a rigid cystoscope and a 22-gauge needle. The product was injected at 20 sites, with each injection delivering 0.5 mL, distributed throughout the bladder [11]. In recent years, more injections were positioned below the equatorial line. To enhance the distribution area of onabotulinumtoxinA, the bladder was filled with 200 mL of saline. Prophylactic antibiotics were administered concurrently with sedation using a third-generation cephalosporin. Following the procedure, the patient was catheterized, and the catheter was removed a few hours later. However, in recent years, no bladder catheter was left in place post procedure, and the bladder was merely emptied.

Post-operatively, patients were assessed by different doctors, at various time intervals.

The primary outcome was efficacy, evaluated through the cessation of the need for pads. Secondary outcomes included the time between injections, determinants of efficacy, and patient satisfaction assessed through an affirmative response to the question "Are you satisfied?". Variables such as age at diagnosis, BMI, prior suburethral sling placement before UUI diagnosis, the number of pads used before and after the intervention, the number of botulinum toxin treatments, the time between each treatment, and patient satisfaction were assessed. Complications were also measured.

The statistical analysis was conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). A descriptive analysis of the sample was performed. Frequencies were expressed in percentages, and continuous variables were presented as means and medians, with their respective standard deviation and interquartile range. Student's *t*-test and chi-square tests were used, considering a p-value < 0.05 as statistically significant. Binary logistic regression was used to evaluate the independent predictive value of the number of pre-injection pads and the previous use of a sling, adjusted for age and BMI, as predictors of the primary outcome.

This study was approved by the ethics committee of the Centro Hospitalar Universitário São João (CES 293/2023).

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study, without investigational intervention.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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DISCUSSION

Epidemiological Data of Urinary Incontinence Among Portuguese Women

As urologists, we frequently manage women with UI and recognize that, despite being a condition sometimes addressed by other overlapping specialties, this broader access does not always translate into effective patient care. What may appear to us as an evident diagnostic issue has frequently undergone inadequate evaluation, with therapeutic measures already in place, often compromising patients quality of life irreversibly.

Furthermore, even among urologists, UI is sometimes regarded as a minor condition, which may lead to a more inattentive approach and, consequently, inappropriate care. Raising awareness about female UI and pleading for new necessary policies is therefore a responsibility of all clinicians.

Although UI is frequently overlooked by physicians managing women, it is also true that very often women believe that incontinence is part of the ageing process, delaying medical attention. However, by the time they seek medical attention, and despite having already developed multiple strategies to cope with the problem, patients recognize that they need a solution. Nevertheless, we regularly encounter women who are eager to try treatments that someone they know has used and liked, regardless of whether those treatments are suitable for their specific type of incontinence or the potential for aggravating their condition in certain cases. Only profound knowledge of the topic and thorough discussion of the cure rates and adverse events with the patients will enables us to serve our patients in the best possible way. Through this knowledge, we can simplify complex information, enabling patients to better understand their condition and involving them in the choice of therapeutic processes. Thus, unraveling evidence that deepens our understanding of this topic has very practical implications. It allows us to better inform patients about their prognosis and may even lead to changes in how this condition—often incurable but manageable—is treated. With long-term treatment, a life significantly hindered by incontinence can become almost normal.

The work presented in this thesis added pertinent information to the existing body of knowledge on these topics. The first challenge was the absence of precise epidemiological data pertaining to Portugal, with our efforts beginning precisely by attempting to clarify and characterize it, as detailed in Chapter 1. This was the first assay to provide a comprehensive overview of the prevalence of female UI in Portugal, linking it to variables that were long suspected to be associated but never conclusively confirmed. The research conducted and presented in this thesis reports that the nationwide prevalence of self-reported UI among women is 9.9%.

The prevalence increased with age, from 2.0% in women aged 18–39 years to 28.9% in women aged 75–85 years. Conversely, UI prevalence declined with higher educational attainment, from 28.2% among women with no formal education to 2.2% in those with over 12 years of education. Similarly, a decrease was observed with higher household income, dropping from 14.4% in the second income quintile to 5.3% in the fifth quintile.

Women with UI exhibited a higher prevalence of comorbidities, particularly hypertension (63.3%), obesity (27.8%), and diabetes mellitus (25.8%). Depression was significantly more common among women with UI (36.9%) compared to those without (15.6%), representing a 66% increase in prevalence. Women with UI also reported higher rates of poor self-rated health (47.8% vs. 13.5%), difficulty concentrating (41.2% vs. 20.7%), and feelings of worthlessness or guilt in the previous two weeks (48.6% vs. 25.4%). All these facts increase healthcare usage by incontinent women, including mental health evaluations, general medical consultations, and high consumption of medication.

These findings challenge assumptions that greater education or income might correlate with higher awareness or reporting rates. Instead, lower education and income may limit knowledge of pelvic health, risk factors, and corresponding preventive measures. Women in lower socioeconomic groups are also less likely to adopt healthy lifestyles and more prone to risk factors like obesity, smoking and higher parity rates, known risk factors for UI. Additionally, physically demanding jobs, and restricted access to healthcare exacerbate UI prevalence in these populations.

This somehow demonstrates that treatment of UI among women involves more than addressing urological conditions alone. A holistic approach is necessary which should take into consideration the management of associated comorbidities, identification of coping attitudes that must be forgotten if quality of life is to be restored. Furthermore, these data highlight the importance of incorporating patients' socio-economic conditions into the treatment approach. However, awareness of UI as a treatable condition, rather than an inevitable consequence of aging, remains low among many patients. This contributes to delays in seeking care, implying that many women never receive proper treatment, relying solely on the use of pads and diapers.

Not being able to treat a condition that disrupts both their quality of life and sense of self-worth, many women are unable to improve their mental health outcomes, increasing consumption of healthcare resources without ever restoring their previous level of wellness. Additionally, they face chronic financial burdens related to containment devices, which have a rarely recognized environmental impact.

Although more prevalent among women with lower education and income levels, UI impacts women across all socioeconomic backgrounds. As such, two main points emerge from this chapter: first, the value of prevention is greater than commonly perceived; second, when prevention proves insufficient, it is imperative to provide the most effective treatment at the earliest opportunity to minimize the overall impact.

Public health initiatives that promote education, improve access to preventive care, and eliminate treatment barriers are essential. These efforts can help to prevent UI, while significantly alleviating the economic burden on healthcare systems. Comprehensive strategies (including early intervention, awareness campaigns, and lifestyle education) are critical to reducing the prevalence of UI and improving outcomes for affected women. In cases where prevention is not feasible, ensuring access to effective treatment can greatly reduce or even eliminate the reliance on containment measures. This, in turn, has the potential to enhance patient well-being while simultaneously easing the associated economic and environmental burdens. This underscores the critical importance of treatment, particularly its long-term effectiveness, in ensuring sustained benefits over time.

Treatment of Female Stress Urinary Incontinence

In Chapter 2, we reflect on the treatment of SUI. It is well established that when conservative treatment fails, surgical intervention is commonly required, with MUS being the most extensively studied options. These procedures are recognized for offering the best balance between efficacy, technical simplicity and adverse events. In an effort to further simplify the MUS procedure single-incision slings were introduced. The second challenge that we faced in our work was the absence of precise data on the treatment of SUI with mini-slings. While they do provide greater simplicity, their long-term efficacy, rather than short-term outcomes, remains a topic of ongoing dispute. The debate surrounding mini-slings is still based on scarce and heterogeneous evidence concerning follow-ups and comparisons with standard retropubic or transobturator slings. In addition, one of the challenges in analyzing the outcomes of sling procedures is the wide variability in outcomes. These range from patient self-reported measures (where, in some studies, the use of just one pad is considered a cure) to physical examinations and urodynamic definitions. This diversity makes it difficult to compare different surgical techniques as well as the evaluation of results of the same surgical approach coming from different centers. Despite these limitations, comparisons among methods and long-term evaluations are critical in this field.

One of the first comparisons between single-incision slings and transobturator standard was carried out in our Institution. Sixty women were randomized to receive a transobturator sling (TVT-O®) or a single-incision sling (MiniArc®). Cure rate was 83% after TVT-O® and 87% after MiniArc®. Improvement was found in 10% and 7% of the patients, respectively. Failures were similar after TVT-O® and MiniArc®, 7%. Both improved at least 15 points in >80% of the patients in six King's Health Questionnaire domains. The postoperative pain score was lower in the MiniArc® group as were the complications. This study had the limitations of a typical phase II trial with a follow-up limited to 12 months [26].

More recently, a larger randomized controlled trial compared mini-slings with MUS among women in UK hospitals during 36 months of follow-up. A total of 298 women were assigned to receive mini-slings (Ajust® and Altis®) and 298 were assigned to

receive MUS (either retropubic or obturator inside-out or outside-in tapes), with the device in both trial groups chosen according to the surgeon's standard practice. The primary outcome was patient-reported success, defined as a response of much improved or very much improved on the Patient Global Impression (PGI) of Improvement questionnaire approximately one year after surgery. At this time point, success was reported by 75.6% in the MUS group and by 79.1% of the women in the mini-sling group. At the 36-month follow-up, success was reported by 66.8% of the women in the standard sling group and by 72.0% in the mini-slings group . Although similar in the short-term to standard slings, long-term duration remained unclear [14].

To contribute to this ongoing discussion, an analysis of our institutional data revealed that after 10 years, the overall objective cure rate was 47%, with participants achieving complete dryness and no reintervention due to SUI or complications. Of the remaining 53%, 2.6% had been operated due to complications, 12.2% due to recurrent SUI and 38.3% were still incontinent. When comparing studies on MUS using the same outcome measures for success, we find, for instance, that the five-year results in the TOMUS trial are comparable, with success rates of 51.3% for retropubic and 43.4% for transobturator slings [27]. However, other studies, at 10-year follow-up reported significantly higher success rates when evaluating standard MUS. Nevertheless, different, less stringent criteria, were used to define cure. Studies on transobturator slings report cure rates exceeding 90% based on negative stress tests; while retropubic slings show cure rates above 80% when defined by the absence of pad usage but still including in the analysis patients who underwent reintervention due to failure or complications [28,29]. In both cases, it is easy to understand why such situations might lead to inflated outcomes. Moreover, giving our defined success measure, the 30% de novo urgency we found, which may simply reflect the ageing of our cohort, may play a confounding role. Consequently, it is not particularly surprising that patient satisfaction results are more comparable across studies. In our report, after a median follow-up of 10 years, 71.4% of women who did not require reoperation rated their continence issues as normal or mild on the PGI of Severity scale, while 63.3% reported being much or very much improved on the PGI of Improvement

scale. Furthermore, over 80% of participants indicated that they would choose to undergo the surgery again, even given their current outcomes. While other studies reveal that patient satisfaction rates remain high after 5 years (79% for retropubic MUS and 85% for transobturator MUS), they decline to approximately 62% after 10 years, reflecting a gradual decrease in efficacy over time [27,29].

More recent data on single-incision slings, although based on a smaller patient cohort and with success primarily defined by a negative stress test, report objective and subjective cure rates of 86.3% and 88.2%, respectively, at a 10-year follow-up [30]. Notably, one of the latest systematic reviews on the topic, including only randomised or quasi-randomised controlled trials, describes that single-incision slings are as effective as transobturator slings and may be comparable to retropubic slings in achieving subjective cure or improvement of stress urinary incontinence at 12 months. Nevertheless, it still underscores persistent uncertainties regarding their longer-term outcomes [31].

Regarding the economic evaluation of SUI surgeries, although single-incision slings are initially less expensive, evidence suggests that, in the long run, there is no significant cost difference between mini-slings and standard slings. Retropubic MUS, however, emerges as the most cost-effective option in the medium to long term [32,33].

Overall, we may state that mini-slings provide a high long-term patient satisfaction, highlighting the fact that eventual small losses, without significant interference in the quality of life, are not perceived by patients as a negative outcome. Notably, subjective cure rates, based on patient-reported outcomes, reflect the ultimate goal of incontinence surgery: the patient's perception of cure.

However, even when acknowledging that single-incision slings provide favorable subjective outcomes, it may be necessary to accept that their objective results are slightly inferior to those of standard MUS. This discrepancy, combined with certain pathophysiological considerations, warrant the consideration that some patients, such as obese women, may not be the ideal candidates for mini-slings. However, this does not mean mini-slings lack utility. They can be particularly valuable in specific groups of patients such as in relatively young women where their insertion preserves the possibility of future standard sling placement. In patients in their early

40s who have exhausted physiotherapy options, mini-slings may offer an attractive opportunity. It is well understood that no sling is likely to last indefinitely. For patients who begin treatment with a standard sling, future options (such as placing another sling, using an autologous sling, or implanting an AUS) tend to be technically more complex and carry higher risks of complications. Mini-slings, on the other hand, allow the possibility of transitioning to a standard MUS 10 to 15 years later, when the patient is still in their 50s or 60s. Eventually, the small size of the synthetic material may allow a simpler removal of the initial mini-sling to avoid the accumulation of synthetic material in the vaginal wall which has been identified as a key factor for vaginal erosions [13]. Additionally, for relatively older patients, mini-slings might hold greater value compared to bulking agents, offering a more durable and effective solution while still maintaining simplicity and safety. Given their competitive cost, they are likely to be economically superior to bulking agents that require repeated injections. A randomized controlled trial between the two methods in elderly women is obviously necessary.

Altogether, our study leads us to state that single-incision slings can serve as an additional therapeutic option to complement the already established arsenal for the surgical treatment of SUI.

Treatment of Urgency Urinary Incontinence

In Chapter 3 we delve into a third challenge, the treatment of UUI, a condition whose prevalence increases in women with advancing age. Furthermore, it is a potential complication of surgical interventions for SUI.

In the treatment of UUI, conservative measures rarely achieve sustained adherence or efficacy in real-life settings, often leading to the necessity of introducing simultaneous pharmacological therapy. While effective, oral pharmacological treatment has interconnected limitations that impact its long-term viability. Efficacy is relatively low, which is actually the first reason for patients to abandon anti-cholinergic medication. In addition, many patients often exhibit poor tolerance to side effects, become frustrated with the need for chronic administration to maintain

efficacy, and, most critically, face an increased risk of cognitive decline due to the cumulative cholinergic load, particularly among older populations.

The next step in the therapeutic ladder includes intravesical botulinum toxin injections and tibial or sacral neuromodulation. Nevertheless, as previously mentioned, the stepwise approach to these treatments remains a subject of some debate. On one hand, T-PTNS and P-PTNS are considered non-invasive or sufficiently minimally invasive to be positioned alongside medication, while intravesical botulinum toxin injections, which have demonstrated superior efficacy in curing UUI compared to antimuscarinic and beta-3 agonist drugs, are usually pushed to a third-line treatment based on the assumption that intervention therapy should follow oral medication [34]. Although this sequencing may be valid in most cases, special attention should be given to the unique characteristics of botulinum toxin treatment.

Despite its established efficacy, studies focusing on botulinum toxin treatment, particularly in idiopathic and female-specific cases, remain limited. This scarcity is even more pronounced when examining patient-reported outcomes or metrics like pad usage, which may better reflect real-world improvements in quality of life than traditional number of incontinence episodes per day or urodynamic parameters. Furthermore, detrusor hyperactivity, a key urodynamic marker for OAB, is not always present in patients and is not essential for diagnosis.

That was the reason why the primary objective of our investigation was to assess the real-world efficacy of botulinum toxin, providing insights directly relevant to clinical practice. After more than 10 years of follow-up, it was apparent that 74.5% of patients reported complete discontinuation of pad usage after treatment with botulinum toxin injections, with the median number of pads used daily dropping from 3 before treatment to 0.

It is important to note that this figure only represents patients who achieved complete dryness, and the remaining 25.5% continued to rely on one or more pads. Among them, some experienced significant improvements that greatly enhanced their quality of life, while 7.2% of patients experienced no improvement, pursuing additional injections to address issues such as dosage or technical factors influencing the initial response.

Our study also showed important clinical observations that might be used to predict treatment success. The main predictors were the number of pads used before treatment and a history of sling placement. Higher baseline pad usage correlated with reduced treatment efficacy, a predictable finding given the therapeutic challenges associated with severe forms of UUI.

Interestingly, patients without a history of sling surgery demonstrated better outcomes after botulinum toxin treatment. This trend of a lower likelihood of achieving a positive response in women who previously underwent a sling procedure was already highlighted in a study conducted at our institution [35].

It is plausible that sling surgery, even in cases with normal post-void residuals and flow rates, increases bladder outlet resistance, leading to functional consequences that may impact outcomes in patients with UUI. In a study from our institution sling operation increased the urinary levels of nerve growth factor which is known to cause sensitization of bladder sensory receptors, leading to a decrease of their threshold for response to bladder filling [36]. For these patients, setting realistic expectations is crucial, as they may be among the most challenging cases yet in greatest need of effective solutions.

As expected, repeated treatments were required once the effects of the initial injection diminished. In 60.3% of cases, repeat injections were administered, with a median of one additional treatment and a median interval of 18 months between the first and second injections. Satisfaction with the initial treatment was a strong predictor of repeated injections, as satisfied patients were significantly more likely to opt for additional procedures in the future. Women who received at least two subsequent injections were also younger at the time of diagnosis compared to those who did not pursue additional treatments.

The interval of 18 months reported between injections was surprisingly long, influenced by logistical challenges, but also by the tail-effect of a prior injection, with some patients still pleased with remaining effect delaying the need for a repeat procedure.

As studies indicate a reduction in urgency severity associated with long-term therapeutic effects, the ideal time frame for patients maintaining regular follow-up, while not uniform for every woman, will likely fall between the standard 6 months

and 18 months [37]. This interval will probably tend to gradually increase over the years as the severity diminishes with repeated treatments, and the patient ages and further adapts to her condition.

Complications associated with botulinum toxin treatment were mild and infrequent. Only 1.1% of patients experienced temporary urinary retention requiring catheterization, and 7.9% reported urinary tract infections, all of which were successfully treated with oral antibiotics. These few side effects, which are easily manageable, are consistent with what has been previously demonstrated [38].

Thoroughly, the reason why this invasive treatment should arguably not be regarded in the same manner as other invasive treatments lies in the fact that it is not as invasive many with same label of invasiveness. The potential complications associated with it are generally minor, consistently temporary, and, importantly, it offers distinct advantages over less invasive alternatives, particularly with regard to cognitive safety.

In light of these considerations, it could be reasonable to prioritize this treatment in certain specific cases, over anticholinergics for particular populations, such as older adults or individuals at risk of cognitive impairment? Furthermore, for patients already undergoing anticholinergic therapy, might transitioning to botulinum toxin provide additional value, especially when considering the cumulative, time-dependent effects of these medications?

Assuming that clinicians may offer third-line treatments in any order, in patients for whom tibial neuromodulation is effective and does not pose logistical challenges for the patient, it may not have an immediate role. However, when compared to sacral neuromodulation, particularly in cases where medication has failed, does it truly make sense to offer SNM to patients unwilling to perform the CIC they risk with botulinum toxin injection, considering that the potential complications of SNM can be more bothersome or severe than the temporary requirement for CIC?

The ROSETTA trial was a significant study comparing the efficacy of bladder injections of onabotulinumtoxinA with SNM in women with UUI. The study concluded that, at 6 months, women in the botulinum toxin group experienced a greater reduction in the daily number of UUI episodes, although the difference was small and of uncertain clinical significance. Notably, the dose of

onabotulinumtoxinA used was 200 units, which is higher than the standard dose used in clinical practice for UUI. However, it is important to mention that only patients who showed at least a 50% improvement during the initial test phase of SNM proceeded in the study, which may have introduced a bias favoring SNM [39]. At two years, the authors reassessed the patients, who were allowed up to two additional injections of botulinum toxin (100 or 200 units, depending on individual circumstances). They concluded that the difference in efficacy between the techniques was no longer statistically significant. However, patients in the botulinum toxin group maintained higher levels of satisfaction and greater treatment endorsement throughout the 24-month period [40]. Finally, the same authors prospectively evaluated the cost-effectiveness of two-stage implantation SNM vs 200 units of onabotulinumtoxinA from the perspective of the healthcare system. They observed that two-year costs were higher for SNM than for onabotulinumtoxinA, a trend that persisted over a five-year period. Based on these findings, the authors concluded that while both treatments were effective for managing UUI, the significantly higher cost of SNM makes it a less cost-effective option compared to 200 units of onabotulinumtoxinA [41].

Thus, does it make sense to offer bladder injection of botulinum toxin and SNM as equally viable treatment options to a patient? Perhaps for young patients, where frequent recurrences requiring repeated injections could disrupt their professional lives and become burdensome, and where the cumulative cost of botulinum toxin injections for the long-term might balance out with the cost of SNM.

However, considering the points mentioned above, it seems reasonable to conclude that for the majority of patients with UUI in Portugal—primarily middle-aged or older women, many of whom rely on the public healthcare system, often with low health literacy and potential difficulty managing the technology involved in SNM, botulinum toxin is undoubtedly a better option. It offers superior cost-effectiveness and frees the patient from dependency on managing a device. Moreover, this approach preserves the option to rescue non-responders with SNM later, ensuring a tailored and stepwise approach to care [25].

Therefore, our work, by reinforcing the notion that we must view the patient as a whole, often even before they become a patient and afterward, without diminishing their condition or the global impact it entails, adds important knowledge to this domain. It strengthens the idea that these women deserve our utmost attention.

The data gathered throughout the different chapters highlight the relevance and impact of personalized treatment, considering not only the clinical condition but also the patient's entire context.

We believe that the long-term goal of this work has been achieved: to provide a thorough epidemiological description of UI in Portugal, gather evidence to further support more comprehensive treatment approaches for both SUI and UUI, and contribute to improved patient outcomes, with potential benefits on a broader scale for society and the environment.

CONCLUSIONS

The main conclusions of this thesis are:

- The nationwide prevalence of self-reported UI among women is 9.9%.
- UI prevalence increases with age from 2.0% in women aged 18–39 years to 28.9% in those aged 75–85 years.
- UI prevalence decreases with higher levels of education, from 28.2% among women with no formal education to 2.2% in those with more than 12 years of education.
- UI prevalence declines with rising household income, dropping from 14.4% in the second income quintile to 5.3% in the fifth quintile.
- Women with UI exhibit a higher prevalence of comorbidities, particularly hypertension (63.3%), depression (36.9%), obesity (27.8%), and diabetes mellitus (25.8%).
- Use of healthcare resources was notably higher among women with UI, including increased general medical consultations, mental health evaluations, and higher medication consumption.
- Effective public health initiatives that promote education, improve access to preventive care, and remove barriers to treatment are essential for addressing UI. These measures can help prevent UI where feasible and ensure timely access to effective treatment where prevention is not possible. The long-term effectiveness of treatment is critical for improving patient well-being, reducing healthcare costs, and mitigating the often-overlooked environmental impact.
- We explored the long-term treatment strategies for both SUI and UUI. When conservative treatment for SUI fails, MUS remain the most extensively studied option due to their balance of efficacy, technical simplicity, and complications. Single-incision slings were developed to further simplify the procedure while reducing the amount of synthetic material used. While short-term efficacy of mini-slings is well-documented, long-term outcomes have been uncertain due to limited studies.

- In our analysis, using stringent cure criteria, we observed a 10-year objective cure rate of 47% in patients with SUI treated with mini-slings, with patients achieving complete dryness and requiring no reintervention for SUI or complications.
- Among the 53% who did not achieve complete cure, 2.6% underwent reoperation for complications, 12.2% for recurrent SUI, and 38.3% accepted the recurrent incontinence. These results are comparable to standard MUS when similar cure criteria are applied.
- Patient satisfaction data also supports the efficacy of mini-slings: after a median follow-up of 10 years, 71.4% of women who did not require reoperation rated their continence as "normal" or "mild" on the PGI of Severity scale, and 63.3% reported being "much" or "very much improved" on the PGI of Improvement scale. Moreover, over 80% of participants indicated they would undergo the procedure again.
- We analyzed the long-term outcomes of botulinum toxin A bladder injections in women with idiopathic UUI in a clinical practice scenario. After 10 years of follow-up, 74.5% of patients reported complete dryness following botulinum toxin A treatment, with the median number of daily pads dropping from 3 to 0. Of the 25.5% who did not achieve complete dryness, only 7.2% showed no improvement.
- Key predictors of treatment success included baseline pad usage and history of sling placement. Higher baseline pad usage was associated with reduced efficacy, while patients without a history of sling surgery demonstrated better outcomes.
- Repeated injections were administered in 60.3% of cases, with a median of one additional treatment and a median interval of 18 months between the first and second injections.
- Patient satisfaction with the initial treatment was a strong predictor of repeat injections. Women receiving multiple injections were also younger at diagnosis compared to those who did not pursue further treatments.

- Complications were minimal, with 1.1% of patients experiencing temporary urinary retention requiring catheterization, and 7.9% reporting urinary tract infections treated with oral antibiotics.
- By addressing gaps in knowledge, this thesis provides relevant insights into the epidemiology and treatment of UI in Portugal. It emphasizes the importance of personalized care, long-term treatment efficacy, and equitable healthcare access. These findings aim to enhance patient outcomes, to reduce societal costs, and to contribute to better policies that promote sustainable, effective UI management.

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