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Characteristics and assisted reproductive outcomes of women with cervical factor infertility

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Resumo

Enquadramento: A infertilidade é uma doença reconhecida pela Organização Mundial de Saúde e afeta um número crescente de pessoas e casais em todo o mundo. Aliada a esta prevalência crescente, surge a necessidade de uma maior e mais minuciosa avaliação de todos os fatores que possam estar envolvidos na sua génese. Embora muitos recursos tenham sido até agora dedicados ao estudo e compreensão dos fatores femininos relacionados com o útero, as trompas e os ovários, sabe-se menos sobre a contribuição dos fatores cervicais para a infertilidade. Neste contexto, e de modo a combater o anteriormente relatado, a presente investigação procurou contribuir para um maior conhecimento e compreensão do fator cervical em casos de infertilidade feminina.

Finalidade: O objetivo deste estudo foi avaliar as características de mulheres com fator de infertilidade cervical diagnosticado na consulta de Apoio à Fertilidade de um hospital terciário, e os seus *outcomes* obstétricos após o tratamento.

Métodos: A presente investigação foi desenvolvida através da realização de um estudo retrospetivo de doentes do sexo feminino em seguimento na Consulta Externa de Apoio à Fertilidade no Centro Materno-Infantil do Norte (CMIN), entre janeiro de 2018 e junho de 2024. Foram recolhidos os processos clínicos, em formato físico e digital, das utentes com diagnóstico de patologias cervicais, e posteriormente utilizado o software *Statistical Package for the Social Sciences* (*IBM SPSS Statistics,* versão 30) para o tratamento dos dados.

Resultados: A amostra incluiu 25 mulheres com infertilidade por fator cervical, com idade média de 35,4 anos e um tempo médio de infertilidade de 4,1 anos. A maioria apresentava infertilidade primária (64%) e nuliparidade (84%). Embora o fator cervical estivesse presente em todas, a maioria das pacientes apresentava etiologia multifatorial, incluindo disfunção ovulatória (40%), fator masculino (24%) e patologia uterina (28%). Em 88% dos casos, a causa cervical foi anatómica, sendo a estenose cervical — frequentemente iatrogénica — a mais prevalente. Apenas quatro mulheres tinham fator cervical isolado. A gravidez foi alcançada em 14 mulheres, sendo que a complicação obstétrica mais comum foi a hemorragia do primeiro trimestre. Identificaram-se seis partos pré-termo, sendo que apenas um caso teve relação direta com a insuficiência cervical. A maioria dos partos foi por cesariana (80%), especialmente em contexto de complicações obstétricas como placenta prévia, oligohidrâmnios e restrição do crescimento intrauterino com cardiotocografia não tranquilizadora.

Discussão: A infertilidade de fator cervical é possivelmente subdiagnosticada, dado que a avaliação inicial padrão da infertilidade feminina raramente inclui uma análise específica da anatomia e funcionalidade do colo uterino. Uma abordagem mais abrangente, que incorpore essa avaliação desde o início, poderá melhorar o diagnóstico e a gestão de casos de infertilidade inexplicada ou multifatorial. Entre as pacientes com infertilidade por fatores uterinos e cervicais — sobretudo nas que apresentavam adenomiose —, observaram-se taxas de gravidez significativamente inferiores às daquelas com fator cervical isolado ou associado a outras etiologias cujo impacto é mitigado pelas técnicas de Procriação Medicamente Assistida (PMA). Estes achados destacam o papel crítico da patologia uterina nos resultados da PMA e sublinham a importância de uma avaliação uterina rigorosa no contexto da infertilidade. O fator cervical esteve implicado em apenas dois casos de complicações obstétricas — um por colo curto e outro por insuficiência cervical —, sugerindo que, nesta população, a patologia cervical não foi um fator determinante dos desfechos obstétricos. Finalmente, as novas diretrizes de rastreio do cancro do colo do útero poderão atrasar o diagnóstico de patologias cervicais, comprometendo a função cervical e a fertilidade, o que reforça a necessidade de maior vigilância clínica para estas futuras pacientes.

Palavras-chave: Colo uterino; Conização; Estenose cervical; Infertilidade; Neoplasia.

Abstract

Background: Infertility is a disease recognized by the World Health Organization (WHO) and affects a growing number of people and couples around the world. Along with this growing prevalence comes the need for a greater and more thorough assessment of all the factors that may be involved in its genesis. Although many resources have so far been devoted to studying and understanding female factors related to the uterus, fallopian tubes and ovaries, less is known about the contribution of cervical factors to infertility. In this context, to combat the above, the present investigation sought to contribute to greater knowledge and understanding of the cervical factor in cases of female infertility.

Aim: The aim of this study was to evaluate the characteristics of women diagnosed with cervical factor infertility at the Fertility Center in a tertiary, as well as their obstetric outcomes after treatment.

Methods: This research was carried out through a retrospective study of female patients being followed up at the Center of Assisted Medical Procreation Center of Centro Materno-Infantil do Norte (CMIN) between January 2018 and June 2024. The clinical files, in physical and digital format, of of women with cervical pathologies were collected. The Statistical Package for the Social Sciences software (IBM SPSS Statistics, version 30) was used to process the data.

Results: The sample included 25 women with infertility due to cervical factor, with an average age of 35.4 years and an average time of infertility of 4.1 years. The majority had primary infertility (64%) and nulliparity (84%). Although the cervical factor was present in all of them, most of the patients had a multifactorial etiology, including ovulatory dysfunction (40%), male factor (24%) and uterine pathology (28%). In 88% of cases, the cervical cause was anatomical, with cervical stenosis - often iatrogenic - being the most prevalent. Only four women had an isolated cervical factor. Pregnancy was achieved in 14 women, and the most common obstetric complication was first trimester bleeding. Six preterm deliveries were identified, only one of which was directly related to cervical insufficiency. Most deliveries were by caesarean section (80%), especially in the context of obstetric complications such as placenta previa, oligohydramnios and intrauterine growth restriction with non-reassuring cardiotocography.

Discussion: Cervical factor infertility is possibly underdiagnosed, given that the standard initial assessment of female infertility rarely includes a specific analysis of the anatomy and functionality of the cervix. A more comprehensive approach, which incorporates this assessment from the outset, could improve the diagnosis and management of cases of unexplained or multifactorial infertility. Among patients with infertility due to uterine and cervical factors - especially those with adenomyosis - pregnancy rates were significantly lower than those with cervical factors alone or associated with other etiologies whose impact is mitigated by Assited Reproductive Technique (ART). These findings highlight the critical role of uterine pathology in the results of PMA and underline the importance of a rigorous uterine evaluation in the context of infertility. The cervical factor was implicated in only two cases of obstetric complications - one due to a short cervix and the other due to cervical insufficiency - suggesting that, in this population, cervical pathology was not a determining factor in obstetric outcomes. Finally, the new cervical cancer screening guidelines could delay the diagnosis of cervical pathologies, compromising cervical function and fertility, which reinforces the need for greater clinical vigilance for these future patients.

Keywords: Cervical stenosis; Cervix; Conization; Infertility; Neoplasia.

Abbreviations and Acronyms

ART – Assisted reproductive tecnhiques

ASA – Antisperm Antibodies

ASRM – American Society for Reproductive Medicine

BMI – Body Mass Index

CIN – Cervical Intraepithelial Neoplasia

ESGE – European Society for Gynaecological Endoscopy

ESHRE – European Society of Human Reproduction and Embryology

FIGO – International Federation of Gynecology and Obstetrics (*Fédération Internationale de Gynécologie et d'Obstétrique*)

FSH – Follicle-Stimulating Hormone

HPV – Human Papillomavirus

ICSI - Intracytoplasmic Sperm Injection

IFV - In Vitro Fertilization

IUGR – Intrauterine Growth Restriction

IUI – Intrauterine Insemination

LEEP – Loop Electrosurgical Excision Procedure

LH – Luteinizing Hormone

PMA – Procriação Medicamente Assistida

PPROM – Preterm Premature Rupture of Membranes

WHO – World Health Organization

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1. Introduction

1.1. Infertility

Historical evidence indicates that, from the earliest times, the human species has exhibited an intrinsic desire for procreation, with infertility often perceived as a deeply distressing condition for certain couples. The involuntary absence of offspring is frequently regarded as a potential destabilizing factor for individual well-being, marital cohesion, and social structure, regardless of cultural context [1].

Infertility is a disease recognized by the World Health Organization, the definition of which varies between clinicians, epidemiologists, and demographers. In fact, the terms and definitions used in fertility care, infertility, and medically assisted reproduction can have varying meanings depending on the context, their use in research or clinical interventions, and differences among populations, making difficult to standardize and compare fertility care interventions and their outcomes, particularly on a global scale. From a clinical and epidemiological point of view, infertility can be defined as a disease of the reproductive system that translates into the inability to achieve a clinical pregnancy after twelve months of unprotected sexual intercourse [2]. The *American Society for Reproductive Medicine* adds to the previously mentioned clinical definition that this disease of the reproductive system can not only make it difficult to achieve pregnancy, but also compromise the ability to carry the pregnancy to term. It also states that the assessment of an infertility condition should take place after the aforementioned twelve-month period, unless factors such as medical history, age (over 35), or physical characteristics warrant earlier evaluation and treatment [2].

Moreover, studies have demonstrated that the longer the duration of infertility, the more challenging it becomes to achieve pregnancy, with a statistically significant reduction observed in clinical pregnancy and live birth rates. Notably, patients experiencing infertility for more than five years show a markedly decreased likelihood of successful outcomes following intrauterine insemination, underscoring the detrimental effects of delayed initiation of fertility treatment[3].

1.1.1. Etiology

According to the last report published by *WHO*, around 17.5% of the adult population – roughly 1 in 6 worldwide – experience infertility in their life [4]. Based on information from the *Portuguese Fertility Association*, infertility affects approximately 300,000 couples in Portugal. Approximately, 30% of cases are related to female causes, another 30% to male causes, 20% to mixed causes and the remaining 20% to unexplained factors [5].

In the female reproductive system, infertility may be caused by: tubal disorders such as blocked fallopian tubes, which are in turn caused by untreated sexually transmitted infections (STIs) or complications of unsafe abortion, postpartum sepsis or abdominal/pelvic surgery; uterine disorders which could be inflammatory in nature (such as endometriosis), congenital in nature (such as septate uterus), or benign in nature (such as fibroids); disorders of the ovaries, such as polycystic ovarian syndrome and other follicular disorders; disorders of the endocrine system causing imbalances of reproductive hormones, for example, pituitary cancers and hypopituitarism; and idiopathic as a diagnosis of exclusion. The relationship between the uterine cervix and fertility is less well studied and understood [6].

Lifestyle factors such as obesity, diet, smoking, and alcohol consumption, along with exposure to environmental chemicals, have been studied as modifiers of infertility [6]. Most of these factors, such as nutritional insufficiency, obesity, stress, chemicals (in the form of pesticides, fertilizers, and industrial products) directly affect the neuroendocrine system, while some other factors, such as alcohol, smoking, caffeine, socioeconomic factors and air and noise pollution, have indirect effects on reproductive health and fertility [7].

1.2. Uterine Cervix Anatomy and Physiology

The cervix, deriving its nomenclature from the Latin word for "neck," constitutes the lower, fibromuscular section of the uterus. The dimensions of the cervix vary, with an average length of 3 to 4 cm and a diameter of approximately 2.5 cm; however, these measurements are subject to fluctuations depending on factors such as a woman's age, her childbearing history, and her hormonal status [8]. Prior to the onset of puberty, the cervix is approximately half to two-thirds the size of the uterus. In adult women, the cervix accounts for approximately one-third of the uterus, while in postmenopausal women, its length approaches that of the uterine body.

It has a cylindrical or conical shape and includes the supravaginal cervical canal (endocervix) along with the vaginal portion that extends into the vagina [9]. The endocervical canal, which runs between the internal and external os, allows communication between the uterus and vagina and reaches a maximum width of 8 mm [8].

The internal os, otherwise known as the isthmus, is the point at which the supravaginal cervix and the uterus meet. The ectocervix, the outer portion of the cervix visible during a speculum examination, is covered with non-keratinized squamous epithelium. The endocervix, located closer to the uterine cavity, is covered with non-keratinized squamous epithelium, whilst the endocervix is lined with columnar epithelium. Over time, squamous cells gradually replace columnar cells in the endocervical glands, resulting in a shift of the squamocolumnar junction upwards. This transformation zone is particularly susceptible to the development of cervical cancer [10].

In terms of reproductive physiology, the cervix, in addition to its role as a barrier against pathogens, protecting the uterus and fallopian tubes from ascending infections, also functions as a channel for the passage of sperm towards the uterus. Structural abnormalities of the uterine cervix, including congenital malformations [11] and iatrogenic acquired deformities [12], have been demonstrated to compromise its functional integrity to a significant degree, thus contributing to poorer reproductive outcomes.

The upward trajectory of sperm through cervical canal toward the uterine cavity is facilitated by the secretion of alkaline cervical mucus by the cervical glands present in the epithelium of the endocervix, serving as a primary defense against external harmful agents. In the female genital tract, mucus is crucial for several biological functions: depending on the stage of the menstrual cycle, it either promotes or inhibits the movement of sperm toward the egg, lubricates the lower genital tract during sexual activity, and keeps the mucosa of the genital tract moist.

The primary source of mucus secreted in the woman’s genital tract is the endocervical epithelium. Water makes up most of the mucus (>95% by weight) and more than 80% of the mucus organic fraction is made up of gel-forming mucins and it is formed when endocervical mucus migrates along the cervical canal to the vaginal cavity. There, it combines with various host-secreted compounds, cellular debris, and vaginal microbiota [13].

The initial phase of the menstrual cycle, characterized by the presence of low levels of estrogen, is referred to as the follicular phase. During this stage, estrogen levels are relatively low, and the cervical mucus is sparse, thick and opaque. This creates an unfavorable environment for sperm survival and motility, forming a barrier to sperm entry into the uterus. The increase in estrogen prior to ovulation supports the secretion of increasing quantities and estrogenic qualities of cervical mucus. The ovulatory phase, marked by the peak of estrogen, is a critical juncture in the menstrual cycle. During this time, estrogen levels surge, prompting significant changes in cervical mucus. This mucus becomes more abundant and waterier, increasing in volume and stretchability. The mucus takes on a clear, egg-white-like appearance, and its pH level is alkaline, making it conducive to sperm viability. The glycoprotein structure of the mucus aligns to form channels, which facilitate the rapid movement of sperm towards the uterus and fallopian tubes. These characteristics are critical for successful fertilization, as they optimize sperm survival and transport during the ovulatory window. After ovulation, in the luteal phase, estrogen levels

drop, and progesterone becomes the dominant hormone. Progesterone then induces the production of thick, sticky, and scanty cervical mucus, which serves as a barrier, hindering sperm penetration and the creation an environment conducive to potential implantation and pregnancy [14].
Cervical factors, as anatomical anomalies or poor cervical mucus quatity/quality, account for 3% of all causes of infertility [15].

1.2.1. Cervical Factor Infertility

1.2.1.1. Congenital Anatomical Cervical Defects

Congenital uterine cervix anomalies are rare developmental abnormalities that occur due to improper fusion or resorption of the Müllerian ducts during embryogenesis. The prevalence of congenital uterine anomalies is estimated to be at 5.5% in the general population, while up to 8.0% in infertile women, 13.3% in women with a history of miscarriage, and 24.5% in those who were infertile that have suffered a miscarriage [16].
The *American Society for Reproductive Medicine* Classification of Müllerian Anomalies categorizes these anomalies into distinct types based on the development of the Müllerian ducts during fetal development. Common cervical anomalies include cervical agenesis, cervical atresia, septate cervix, and double cervix, often associated with uterine malformations such as a bicornuate or didelphys uterus. Congenital anomalies of the cervix are more commonly associated with other uterine and vaginal anomalies [17]. Nevertheless, cases of complete or partial cervical duplication with a normal uterus, as well as rare Müllerian anomalies, have been documented [18].
Cervical agenesis is an anomaly in which the cervix is partially or completely absent. It is a relatively rare form of Müllerian abnormality and its prevalence ranges from 1/80,000 to 1/100,000, and in about 50% of these cases it coexists with congenital vaginal agenesis [19]. If not diagnosed and definitively treated early, it can lead to primary amenorrhea, hematometra, and severe dysmenorrhea, resulting in significant morbidity. [20]. Müllerian agenesis occupies the end of the spectrum since it results in inability to conceive [21].
Cervical atresia is a rare congenital reproductive tract abnormality characterized by the blockage of the cervical canal due to improper development or failure of canalization of the Müllerian ducts during fetal growth. Based on the American Fertility Society classification system and the *European Society of Human* Reproduction and Embryology (ESHRE) and the *European Society for Gynecological Endoscopy* (ESGE) classification system for female genital tract abnormalities, the congenital vaginal atresia is classified as complete and partial atresia [22]. The impact on a woman's reproductive potential varies depending on the extent and nature of the cervical malformation [17].
A septate cervix, characterized by a fibrous or muscular division within the cervical canal resulting from incomplete resorption of the Müllerian ducts during fetal development, is the most common Müllerian anomaly. It accounts for 75% of all Müllerian anomalies [23], 35% of all anatomical uterine anomalies, and has a prevalence of 1% to 2% in the general population [21,24]. However, some researchers conclude that the latest classification systems have led to an overdiagnosis of uterine septum [25].
A double cervix, also known as cervical duplication, is a rare congenital anomaly in which a woman has two distinct cervices as a result of incomplete fusion of the two Müllerian ducts during fetal development. A double cervix is often associated with other Müllerian anomalies, such as a uterus didelphys, where there are two separate uteri, or occasionally, a bicornuate uterus.
These congenital anomalies have been identified as potential causes of infertility [26], pregnancy losses [27] and preterm delivery [28], however outcomes may vary depending on the severity of the defect [24,29].

1.2.1.2. Iatrogenic Cervical Infertility

Procedures such as cryotherapy and cervical conization, though essential for the management of cervical precancerous lesions and invasive cervical cancer, may inadvertently compromise cervical integrity and function [12].

Premalignant lesions of the cervix, or Cervical Intraepithelial Neoplasia (CIN), are noninvasive dysplastic lesions characterized by the abnormal growth of epithelial cells on the surface of the cervix with the potential to progress to invasive cervical cancer.

Cervical precancer can be effectively treated with both excisional techniques (Loop Electrosurgical Excision Procedure and cold knife conization) and ablative techniques (cervical cryotherapy, laser ablation). Although ablative therapies are now used far less frequently than LEEP, they are nevertheless viable alternatives for treating cervical precancer in women of reproductive age since they have less of an effect on unfavorable obstetric outcomes 30. In addition, a retrospective study carried out in 2020 by Zhang et. al, showed the adverse pregnancy outcomes post-conization were associated with internal orifice, damage destroyed mucus-producing cervical gland, and cervix stenosis, which may obstruct sperm migration and hinder successful fertilization [31]. Furthermore, literature indicates that cervical stenosis, by impairing access to the endocervical canal, can lead to increased difficulty during embryo transfer and lower implantation rates, for which cervical dilation may represent an effective therapeutic strategy to facilitate catheter placement and improve reproductive outcomes[32].

Cervical cancer remains a major global health concern, notwithstanding significant advancements in prevention. Cervical cancer is the third most common cancer of the female genital tract, with a peak incidence in women between 35–44 years of age [33]. Persistent infection with high-risk human papillomavirus genotypes—notably HPV-16 and HPV-18—constitutes the primary etiological factor [34]. Once the diagnosis is confirmed using colposcopy with cervical biopsy, invasive cervical cancer should be staged with revised (2018) FIGO staging [35] to determine the appropriate treatment and likely prognosis. Although surgery (e.g., conization, trachelectomy, hysterectomy) may be appropriate for early-stage disease, management options for advanced disease include concurrent chemoradiotherapy, systemic chemotherapy, and palliative radiotherapy [36].

Previous obstetric or gynecological trauma, as previous conizations, and short cervical length are also proven risk factors for cervical insufficiency [37]. When a woman's cervix has a structural or functional problem that prevents her from supporting a full-term pregnancy, this is known as cervical insufficiency [38]. In this matter, cervical insufficiency is usually diagnosed in patients with cervical dilation prior to 24 weeks of pregnancy or in those with history of preterm birth in the second trimester or pregnancy loss associated with painless cervical dilation [39]. Although a short cervix alone is not diagnostic of cervical insufficiency, some profissionals make this diagnosis if the patient has had a previous preterm birth or pregnancy loss between 16 and 36 weeks, especially if the cervix is short before 24 weeks in the current pregnancy [40]. A serial cervical ultrasound monitoring between 16 and 24 weeks' gestation is recommended in women with risk factors: daily vaginal progesterone is advised if cervical length <25mm without others underlying conditions; on the other hand, if the short cervix is associated with protrusion of membranes, anterior pre-term labor or progressive shortening of the cervix, cerclage is recommended [41].

1.2.1.3. Cervical Mucus Anomalies

Cervical mucus is a heterogeneous mixture of secretions produced by the endocervical mucous glands. From an ultrastructural point of view, cervical mucus is a complex biphasic fluid made up of two main components: cervical plasma, a low molecular weight fraction, which mainly contains trace elements such as zinc, copper, iron, manganese, selenium, sodium and chlorides, as well as low molecular weight organic compounds such as glucose and amino acids, and soluble proteins including albumin and globulins; and a high molecular weight fraction, corresponding to the gel phase, made up of a network of glycoproteins called mucin, whose composition and degree of glycosylation vary throughout the menstrual cycle, directly influencing the physical properties of the mucus [42]. The secretion of cervical mucus responds to a series of hormonal fluctuations during the menstrual cycle, leading to cyclical changes that affect its biochemical and biophysical properties [43].

There are several types of mucus, as characterized by Odeblad, E. [44]:

- Type E - thin and watery mucus (with approximately 98% of water), also called as fertile mucus. During the follicular phase, as estrogen increases, the mucus becomes more abundant, clear, and elastic, often experienced by women as a clear, stretchy, and slippery discharge, creating an ideal environment for the survival and mobility of sperm, thus facilitating fertilization [45,46] .
- Type G - thick and sticky mucus. Under the influence of progesterone, the water content decreases to approximately 90% and the mucus becomes more viscous. After ovulation, the subsequent rise in progesterone causes an abrupt decrease in mucus secretion and it becomes thicker, opaque, and sticky, creating a barrier that makes it difficult for sperm to pass through, which corresponds to the non-fertile period of the cycle [47].

Cervical mucus abnormalities have been shown to have an impact on fertility. For instance:

Chronic cervicitis is associated with alterations in cervical mucus, with its composition varying depending on the type, degree, and duration of the inflammatory process. Studies show that inflammation affects the secretory function of the cervical glands, leading to the production of a thick, opaque or sparse mucus, often loaded with leukocytes and other inflammatory cells, which creates a physical and immunological barrier to sperm [48]. As a result, cervical infections such as those caused by sexually transmitted microorganisms (Chlamydia trachomatis, Neisseria Gonorrhea, Trichomonas vaginalis and Mycoplasma hominis) may lead to a hostile cervical environment [42].

Women with Cystic Fibrosis are also unable to produce the elastic, watery mucus necessary for optimal sperm penetration. Cystic Fibrosis results from a mutation in the gene responsible for the Cystic Fibrosis Transmembrane Conductance Regulator protein, causing chloride to become trapped inside the cells. Since chloride has a negative charge, it generates a disparity in the electrical potential across the cell membrane, leading to sodium entering the cell. Consequently, the reduced movement of water from the intracellular to the extracellular spaces results in thicker, less fluid mucus, negatively affecting sperm transport [49]. It is important to note that with advances in the treatment of cystic fibrosis, there are increasing reports of partial normalization of cervical secretions and even spontaneous pregnancies in women with CF - which represents a promising change in the reproductive outlook for these patients [50].

Additionally, numerous studies have indicated that clomiphene citrate, commonly utilized to promote follicle due to its structural similarity to estrogen, can negatively influence cervical mucus. Unlike estrogen, clomiphene citrate binds to nuclear estrogen receptors for prolonged durations, ultimately depleting these receptors by disrupting their usual regeneration process. The blockage of estrogen receptors at the peripheral level - including the cervix - can lead to the production of scarce, thick and less elastic cervical mucus, with characteristics that are not favorable for sperm penetration [51]. In fact, it was already demonstrated in 1989, in a study conducted by Marchini et al., that up to 60 percent of women using clomiphene experience

changes in cervical mucus, which negatively impact fertility, especially when the treatment is prolonged or administered at high doses [52] .

Furthermore, Jones et al. investigated the presence of nicotine in the cervix of women exposed to passive smoking: high levels of nicotine were detected in cervical washings from non-smoking women exposed to passive smoking, demonstrating that nicotine inhaled through the environment can directly reach cervical tissues, even in women who do not smoke actively [53]. McCann et al. compared the levels of nicotine and cotinine (a nicotine metabolite) in the cervical mucus of three groups: smokers, passive smokers, and nonsmokers: the smokers had significantly higher levels, but the group exposed to passive smoking also had higher concentrations than the non-smokers. These findings suggest that exposure to nicotine, whether active or passive, results in local accumulation in cervical secretions, which can adversely affect reproductive functions - including the quality of cervical mucus [54]. In addition, a retrospective study of 901 infertile women and 1,264 pregnant women conducted by Phipps et al. showed that smoking is associated with an increased risk of infertility due to cervical factors (relative risk of 1.7; 95% confidence interval: 1.0 to 2.7), reinforcing the hypothesis that smoking directly compromises the functionality of cervical mucus. Nevertheless, the exact mechanism by which it occurs is still unclear [55].

1.2.1.4. Acquired cervical defects

Uterine fibroids, or uterine leiomyomas, are non-cancerous smooth muscle tumors in the uterus that impact women in reproductive ages. fibroids may also be associated with reproductive problems such as infertility, recurrent pregnancy loss, and adverse obstetric outcomes: Coronado et al. conducted a study, that revealed that uterine fibroids increase the likelihood of various obstetric complications, including placental abruption, early bleeding, dysfunctional labor, breech presentation and caesarean section [56]. A year later, Benson et al. demonstrated that uterine fibroids are associated with an increased risk of spontaneous pregnancy loss and a greater likelihood of caesarean section, especially in cases with multiple fibroids [57]. More recently, Whynott et al. systematically reviewed the literature on the impact of uterine fibroids on infertility and concluded that the localization of fibroids is crucial in assessing their impact on fertility. Submucosal fibroids have the most significant negative effect, while subserosal fibroids have minimal impact [58].

Cervical fibroids develop in the wall of cervix. Cervical fibroids can affect the supravaginal or vaginal portion of the cervix. Supravaginal fibroids can be central surrounding the entire cervical canal and lying centrally in the pelvis displacing the uterus superiorly. They can also be unilateral or bilateral, can be intramural or subserosal, and can be lying in the pelvis [59]. In 1998, Tiltman examined 661 consecutive total hysterectomy specimens, macroscopically and microscopically. Myometrial leiomyomas were present in 427 uteri (64.6%) but cervical leiomyoma were present in only 4 (0.6%) [60]. Likewise, newer research indicated that leiomyomas occur in 20% of those in reproductive age, yet cervical ones make up only 1-2% of the overall total [61]. If cervical fibroid increases in size can lead to obstructive symptoms as urinary retention, constipation, menstrual abnormalities, and well as dyspareunia and postcoital bleeding [62].

The traditional mechanisms by which fibroids are thought to be related to fertility problems are associated simply with their physical presence in the uterus. Fibroids may impede sperm or egg transport through displacement of the cervix or obstruction of the fallopian tubes and pouch of Douglas. Implantation may be affected by deformity of the cavity but increased contractility of the myometrium and a chronic inflammatory response by the endometrium to underlying fibroids may also be important. Many studies look at a single mechanism but it is most probably a combination of factors that contributes to any associated fertility difficulties [63,64].

Cervical polyps are the second most frequently identified polyps after endometrial polyps, arising from the papillary growth of columnar epithelial tissue encircling a fibrovascular stromal core that may contain glandular or squamous epithelium [65]. They occur more often in females who have given birth or are postmenopausal and are typically benign asymptomatic lesions. Cervical polyps can be classified as endocervical, located within the cervical canal, or ectocervical, found on the external surface of the cervix as defined by the transformation zone. Endocervical polyps occur more frequently than ectocervical polyps, primarily in premenopausal women. Levy et al. indicated that endocervical polyps are present in approximately 2-5% of individuals [65]. The pathophysiology is not clearly understood but possible pathogenesis include chronic inflammation, hormonal stimulation or cervical blood vessel congestion [66]. Approximately 60 - 70% of cervical polyps do not present symptoms, particularly in postmenopausal women [67]. Symptomatic cervical polyps typically present as intermenstrual, post-coital, or postmenopausal bleeding because their friability on visual inspection can easily cause bleeding upon contact [68]. The study by Hirayama et al. investigated the association between cervical polyps in early pregnancy and the risk of late miscarriage and spontaneous preterm labor and the results showed that the incidence of late miscarriage and spontaneous preterm labor was significantly higher in the group of women with cervical polyps detected early in pregnancy compared to the group without polyps and the presence of cervical polyps in early pregnancy was identified as an independent risk factor for late miscarriage and spontaneous preterm labor before 28, 34 and 37 weeks of gestation [69]. In the same year, the

study by Wakimoto et al. also investigated the relationship between cervical polyps not removed in early pregnancy and the risk of spontaneous preterm labor and concluded that the presence of cervical polyps detected before 12 weeks of gestation, even when managed expectantly (without removal), is associated with a significant increase in the risk of spontaneous preterm labor before 34 weeks [70].

Based on the articles by Schrager et al. (2022) and Kho et al. (2021), adenomyosis is frequently observed in association with other benign uterine pathologies, particularly uterine fibroids and endometrial polyps. This coexistence may reflect shared pathophysiological mechanisms, notably estrogen hyperresponsiveness and alterations in the endometrial and myometrial architecture, which promote disordered tissue growth within the uterus. According to Schrager et al., the concurrent presence of adenomyosis and fibroids is a common finding, with both conditions contributing to symptoms such as abnormal uterine bleeding, dysmenorrhea, and infertility[71,72]. Interestingly, a study conducted by A. Xholli et al. in 2023, was the first study to demonstrate, using cervical elastography techniques, that women with adenomyosis have an increased OCI stiffness. Chronic inflammation and subsequent fibrosis associated with the disease can lead to increased rigidity of the cervical canal, reducing its compliance and impairing its physiological permeability to spermatozoa. Therefore, infertility in the context of adenomyosis should be regarded as multifactorial, encompassing not only endometrial and myometrial dysfunction but also structural and functional impairment of the cervical canal [73].

1.2.1.6. Immune factors (e.g., anti-sperm antibodies)

Immune infertility, characterized by the inability to conceive due to immune-mediated mechanisms, has been linked to the presence of anti-sperm antibodies. *Naz et al.* reviewed clinical data showing that up to 9-36% of infertile couples may have ASAs as a contributing factor depending on the reporting center [74]. Anti-sperm antibodies in cervical mucus interfere with sperm motility, reducing their ability to effectively progress towards the oocyte. AS et al. described three main mechanisms by which ASAs affect fertility, interfering with sperm motility and their ability to fertilize the oocyte: Sperm agglutination (which prevents them from progress individually), immobilization of sperm by blocking ion channels that are essential for flagellar movement, and interference in the interaction with the zona pellucida (the ASAs covering their surface can prevent them from binding to specific receptors in the zona pellucida, interfering with the acrosome reaction) [75].

These antibodies, which are produced by both men and women, have been identified as a contributing factor to infertility since women with detectable ASAs in cervical mucus had significantly lower pregnancy rates, highlighting the immunological impact on natural fertility [76].

2. Investigation

2.1. Objectives

This study aims to evaluate the outcomes of fertility treatments in women diagnosed with cervical pathologies, investigating the influence of these conditions on gestational and obstetric outcomes.

To achieve this goal, the success rate of different fertility treatments applied to women with cervical pathologies will be analyzed. This parameter will be measured based on the pregnancy rate confirmed by positive β-HCG and its progression throughout pregnancy.

In addition, the study aims to evaluate pregnancy complications, such as miscarriage, cervical incompetence, the threat of preterm labor and the need for additional therapeutic interventions.

Another essential parameter to be analyzed will be gestational age at delivery given the predisposition of women with cervical pathologies to premature birth. The type of delivery will also be analyzed, investigating the proportion between vaginal deliveries and caesarean sections, as well as the determining factors for the indication of surgical delivery. Finally, birth complications and length of hospital stay will be examined.

2.2. Methods

A retrospective study to examine the impact of cervical factors on the outcomes of Assisted Reproduction Treatments between January 2018 and June 2024 from a northern Portugal tertiary public center was designed.

Ethics Committee of the Centro Hospitalar Universitário de Santo António, EPE (CHUdSA) and the Instituto de Ciências Biomédicas Abel Salazar (ICBAS) were formally contacted before data collection to obtain permission to gather data and obtain approval for this study.

After receiving authorization, clinical records, both in physical and digital format, of the patients with cervical pathologies followed up in a Medically Assisted Procreation consultation at the Centro Materno Infantil do Norte were collected between January and February 2025.

The inclusion criteria for the study group included women with diagnosed cervical pathology who underwent fertility treatment during the period mentioned. No exclusion criteria were considered. Overall, 25 patients with cervical factor infertility were treated in this timeframe.

Furthermore, the Statistical Package for the Social Sciences software (IBM SPSS Statistics, version 30) was used to process and statistically analyze the data collected. Initially, descriptive analyses were carried out on the variables under study, allowing for a detailed characterization of the sample. Finally, the findings of this study were connected to the outcomes of previously published articles.

Because of the reduced N in this study, data interpretation was focused on descriptive analyses. By using this methodological precaution, the limited sample size was intended to prevent erroneous interpretations or unwarranted generalizations.

2.3. Results

2.3.1. Sample description

This study included a total of 25 patients. Data collected regarding age, BMI, gynecological and obstetric history and details about the couple infertility (time and type of infertility) are reported in Table I.

The average age of the women was 35.36 years (SD = 3.23), with a range of 11 years. Regarding Body Mass Index, the average was 24.19 kg/m² (SD = 4.19), varying within a range of 16.0 kg/m².

Regarding obstetric history, 16 women (64%) have never been pregnant, while 4 (16%) have had one pregnancy, 3 (12%) have had two and 2 (8%) have had three pregnancies. Thus, and regarding the type of infertility, primary infertility was predominant: primary infertility was recorded in 16 women (64%), while secondary infertility only in 9 women (36%).

Regarding parity, 21 women (84%) had never given birth, while 4 (16%) had given birth at least once. By comparing parity with the type of infertility, we observe that five women had experienced miscarriages in the past.

Finally, the average time of infertility was 4.14 years (SD = 1.64), with a range of 6.5 years.

2.3.2. Infertility Etiology

Table II provides an overview of the different causes of infertility. In the evaluated cohort of 25 women with cervical factor infertility, the concomitant presence of other infertility factors was verified.

Ovulatory dysfunction was identified in 40% of participants, male factor infertility in 24%, and uterine factor infertility in 28% (6 women with concomitant adenomyosis and 1 with septated uterus). Tubal factor infertility accounted for 8% of cases, thyroid disease was associated with infertility in 16%, and other causes comprised the remaining 8% of the cohort.

It is important to note that multiple etiological factors were frequently concomitant within the same individual, highlighting the multifactorial nature of infertility in this population: 15 women had two infertility factors combined, 3 women had 3 infertility factors and other 3 had 4 infertility factors. Only 4 of the 25 women had cervical infertility as their sole diagnosed condition.

2.3.3. Cervical Factors

An outline of the different etiologies of cervical factor infertility can be found in Table III. Of the 25 individuals evaluated, 22 (88 %) had infertility attributable primarily to anatomical cervical abnormalities.

Among the 19 cases of cervical stenosis, nine were iatrogenic — related to prior diagnostic or therapeutic procedures such as cervical conization. Of these, two patients had undergone treatment for cervical cancer and seven for cervical intraepithelial neoplasia. Cervical stenosis was also identified in 6 patients (24%) presenting with concomitant adenomyosis. The remaining 4 cases (16 %) were idiopathic, identified either during routine fertility work-ups or following difficult intrauterine inseminations in women without any known cervical pathology.

In a few exceptional instances, other structural anomalies were also noted, including a cervical neurofibroma, an incompletely septated uterine cervix, and cervical shortening after trachelectomy.

Finally, given that thyroid disease can compromise the integrity of cervical mucus, 3 out of 25 patients (12%) who exhibited no identifiable cervical anatomical abnormalities but had thyroid disease were nevertheless considered to have a probable cervical factor contributing to their infertility.

2.3.4. Assisted reproductive techniques

Table IV presents data on the number of fertility treatment attempts and the outcomes of the final reproductive technique employed.

Among the 25 patients assessed, the mean number of prior fertility treatment attempts was 3.56 (range 1–7; SD 1.76).

Of the seven patients presenting with concomitant uterine and cervical factor infertility — six diagnosed with adenomyosis and one with septated uterus— only two achieved clinical pregnancy. In contrast, among the eighteen patients with isolated cervical factor or cervical factor associated with other etiologies of infertility whose impact was effectively mitigated through ART, twelve achieved pregnancy.

With respect to the assisted reproductive tecnhiques (ART) employed in the latest attempt, intrauterine insemination (IUI) was used in 4 cases (16%), 3 of which (12%) resulted in pregnancy, and 1 of which (4%) did not. In total, 11 individuals (44%) had in vitro fertilization (IVF), of whom 7 (28%) became pregnant and 4 (16%) did not. Ten cases (40%) involved the intracytoplasmic sperm injection (ICSI) technique; four (16%) of these cases resulted in pregnancy, four (16%) did not, and two (8%) were cancelled due to intracytoplasmic anomalies in a single ovocyte. Overall, 14 women became pregnant, resulting in an effectiveness rate of 56%.

2.3.5. Pregnancy complications

Table V presents an overview of pregnancy-related complications. A total of fourteen ladies became pregnant. However, three of them were followed up at a different hospital, so no data was available for these cases. Consequently, the information only covers eleven pregnant women. Of the 11 total pregnant women, one spontaneous abortion on the first trimester was registered, as well as 2 placentas previas, 2 preterm premature rupture of membranes, 2 intrauterine growth restriction, one short cervical length and one preeclampsia case. First-trimester bleeding was the most common complication, occurring in a total of 7 women.

Both patients with placenta previa were diagnosed by routine obstetric ultrasound during prenatal care. Consequently, an elective caesarean section was scheduled at 37 weeks' gestation for each. No risk factors were identified in the first patient, while advanced maternal age (38 years) was the sole risk factor in the second, warranting closer obstetric monitoring.

In the two women who experienced preterm premature rupture of membranes, the event occurred at 33 weeks and both women were admitted to the obstetrics department. They received intravenous antibiotics and corticosteroid therapy for fetal lung maturation. None of them had identifiable risk factors for preterm premature rupture of the membranes.

Regarding fetal growth restriction, one of the patients with a diagnosis of intrauterine growth restriction developed preeclampsia during pregnancy and had a documented history of thrombophilia due to protein C deficiency. Both preeclampsia and hereditary thrombophilic disorders are well-established risk factors for uteroplacental insufficiency, the principal underlying etiology of IUGR. The second patient with IUGR during pregnancy presented to the emergency department due to decreased perception of fetal movements. Obstetric ultrasound also revealed oligohydramnios and IUGR. The same woman was diagnosed with short cervical length at 32 weeks pregnant and treatment with vaginal progesterone was initiated.

2.3.6. Pre-term Labor *versus* Full-Term Labor

Table VI illustrates the association between cervical pathology type and the timing of delivery, according to whether they experienced preterm or full-term delivery. Among these 10 patients, six had preterm labor and four delivered at term.

In the subgroup with cervical stenosis of iatrogenic origin, all women who conceived subsequently experienced preterm labor, and one patient with adenomyosis delivered before 37 weeks. Among those with idiopathic cervical stenosis, one had preterm deliveries and one carried the pregnancy to term.

The patient with cervical neurofibroma and the one with an incompletely septated cervix both delivered after 37 weeks of gestation.

Lastly, one patient was classified under the 'other' category, with suspected altered cervical mucus quality possibly related to thyroid dysfunction; this patient also had a term delivery.

Among the six women who experienced preterm birth in this study group, five delivered prematurely due to complications unrelated to cervical factors and one of them delivered prematurely due to cervical insufficiency. This patient, previously diagnosed with cervical idiopathic stenosis, presented to the emergency department at 23 weeks and 6 days of gestation with blood-stained vaginal discharge and was diagnosed with cervical insufficiency due to cervical dilation. She remained hospitalized for approximately two months, during which she received corticosteroids for fetal lung maturation, along with antibiotics, tocolytics, and magnesium sulfate. Delivery occurred at 33 weeks of gestation.

It is important to note that the patient diagnosed with a short cervix at 32 weeks of gestation ultimately had a preterm delivery unrelated to cervical insufficiency: delivered at 36 weeks and 5 days due to severe intrauterine growth restriction and oligohydramnios.

2.3.7. Types of Delivery

An overview of hospitalization duration (pre- and post-delivery) and the types of childbirth procedures performed is presented in Table VII. The total number of inpatient days encompasses admissions occurring during pregnancy, as a result of obstetric complications, until puerperium. The average number of days of hospitalization was 13.5 days, with a standard deviation of 19.962 days. The range of hospitalization days was 64 days, since there was one woman who spent a total of 67 days in hospital for fetal lung maturation, along with antibiotics, tocolytics, and magnesium sulfate. Similarly, other woman spent 23 days with the same therapeutic regimen. These two cases constitute notable outliers regarding the number of hospitalization days, thereby disproportionately increasing the mean hospital stay within the cohort.

Regarding the birth method, two of the ten expectant mothers experienced eutocic labor: one of them had an eutocic twin birth at 35 weeks and 4 days, complicated by a second-degree perineal laceration. The second one presented to the emergency department with moderate headache and high blood pressure and was hospitalized due to gestational hypertension and suspected IUGR. Three weeks later, she experienced an eutocic vaginal birth at 30 weeks, and a severe pre-eclampsia during the postpartum phase was diagnosed.

Furthermore, three women underwent elective caesarean: two of them at 37 weeks due to placenta previa detected on standard prenatal ultrasound examinations; and, additionally, one patient at 36 weeks and 6 days, after an ultrasound scan carried out the day before in the emergency department revealed oligohydramnios and IUGR.

Five women (50%) had emergency cesarean sections performed. Two of them was due to PPROM at 34 weeks: a primigravida with a dichorionic-diamniotic pregnancy with the first fetus in pelvic presentation, and the second one also a nulliparous with a singleton pregnancy with pelvic presentation.

One pregnant woman presented with preterm premature rupture of membranes at 33 weeks and was hospitalized for monitoring and administration of corticosteroids. She underwent an urgent caesarean section at 34 weeks due to suspected chorioamnionitis associated with a non-reassuring fetal condition.
Finally, two women underwent an urgent caesarean section due to arrested active phase.

4. Discussion

The objective of this study was to conduct a descriptive analysis of a population of women attending a fertility clinic in whom cervical factor infertility was identified. Additionally, the study aimed to characterize the obstetric outcomes associated with the fertility treatment modalities implemented, thereby providing insight into the reproductive prognosis and effectiveness of therapeutic interventions in the context of cervical factor infertility.

In what concerns the first objective, the mean age of the participants was 35.36 years, which is consistent with the national average age of infertile women[5], with an average BMI of 24.19 kg/m². Furthermore, 64% were nulligravid and 84% were nulliparous. The elevated rates of nulligravidity and nulliparity in this cohort highlight the clinical importance of early recognition and individualized management in cases of female infertility, particularly when cervical factor is involved. Cervical factor infertility is presumably underdiagnosed, as the standard initial evaluation of female infertility does not typically include a focused assessment of cervical anatomy and function. As a result, subtle or functional cervical abnormalities may potentially remain undetected, especially when concurrent infertility factors, such as ovulatory, tubal, or male components, are present and prioritized in the diagnostic algorithm. A more comprehensive and structured approach that includes targeted cervical evaluation from the outset may improve diagnostic accuracy and contribute to more timely and effective management in women with unexplained or multifactorial infertility.

Notably, the prolonged duration of infertility highlights the chronicity of reproductive challenges within this population and reinforces the need for sustained clinical surveillance and intervention. Moreover, these data indicate that a substantial proportion of couples face prolonged periods of uncertainty and struggle prior to seeking or initiating assisted reproductive treatments, which can have significant implications in what concerns the effectiveness of interventions, as described by Chenyang, et al. (2024)[3].

In this study, the majority of infertility cases attributed to cervical factor were related to anatomical abnormalities, with cervical stenosis accounting for 76% of the evaluated cases. The iatrogenic etiology was significant, primarily associated with prior procedures such as cervical conization, treatment for cervical intraepithelial neoplasia, and cervical cancer, highlighting the impact of medical interventions on cervical integrity[31]. Concurrently, a considerable proportion of cases remained idiopathic, underscoring the need for thorough investigation during infertility assessments.

In the study, three women with idiopathic infertility were considered to have a probable cervical factor contributing to their infertility due to thyroid disease (both hypothyroidism and hyperthyroidism), despite the absence of detectable anatomical cervical abnormalities, which is attributed to the detrimental effects of thyroid dysfunction on the quality of cervical mucus.

With respect to obstetric outcomes, of the 25 women monitored, 14 managed to become pregnant, which represents a success rate of 56%. This result can be considered clinically relevant, showing a high rate of effectiveness of the therapeutic protocol implemented. Notwithstanding, the complexity of their reproductive route may be reflected in the fact that most patients assessed had undergone several prior fertility treatment attempts. This finding is consistent with the literature, which indicates that anatomical cervical defects can lead to increased difficulty during embryo transfer and, in cases where the defect manifests as cervical stenosis, cervical dilation may be considered as a potential intervention, given its demonstrated efficacy in improving embryo transfer outcomes[32].

Of the seven patients presenting with concomitant uterine and cervical factor infertility — six diagnosed with adenomyosis and one with septated uterus— only two achieved clinical pregnancy. In contrast, among the eighteen patients with isolated cervical factor or cervical factor associated with other etiologies of infertility, whose impact was effectively mitigated through ART, twelve achieved pregnancy. These findings strongly suggest that the presence of uterine pathology, particularly adenomyosis, significantly impairs reproductive outcomes[73],

even when other contributory factors are adequately addressed. This underscores the critical role of uterine structural and functional integrity in determining the success of ART, given its fundamental importance for endometrial receptivity, embryo implantation, and gestational progression. Thus, reproductive efficacy must be understood within a multifactorial framework, wherein uterine pathology constitutes a pivotal limiting factor to successful embryo implantation. Importantly, such cases of adenomyosis are increasingly identified owing to the thorough and sophisticated uterine diagnostic evaluation currently employed in the context of infertility workup, allowing for the detection of uterine abnormalities that might otherwise remain unrecognized.

The use of varied assisted reproductive techniques — IUI, IVF, and ICSI — reflects an individualized approach tailored to the specific infertility factors of each couple. It is important to highlight that the high prevalence of second-line medically assisted reproduction techniques, such as IVF and ICSI, observed in this cohort, is justified not only by the presence of concomitant male factors, but also by the failure of prior attempts using first-line treatments, such as IUI. Although IUI demonstrated a relatively high success rate (75% of attempts resulted in pregnancy), it was employed in a limited number of cases. IVF and ICSI, which together accounted for the majority of treatment attempts, showed moderate pregnancy rates, underscoring the ongoing challenges associated with these therapeutic modalities.

First trimester bleeding was the most prevalent pregnancy complication in this population, occurring in 64% of the studied women. The rate of first trimester bleeding observed in this study was higher than that reported in the general population in previous studies [77]. Although there are currently no studies demonstrating a direct relationship between cervical pathology and an increased risk of hemorrhage during pregnancy, it can be speculated that the presence of cervical alterations may compromise the mucosal and vascular integrity of the cervix, thereby increasing susceptibility to hemorrhage.

Regarding the type of delivery carried out, none of these obstetric decisions were directly attributable to cervical pathology. The indications for cesarean delivery were primarily obstetric in nature, including placenta previa, fetal growth restriction, oligohydramnios, and hypertensive disorders of pregnancy. This observation suggests that, despite the underlying cervical factor contributing to infertility in these patients, it did not appear to influence the mode of delivery, nor did it constitute an obstetric indication for surgical intervention in this population.

Additionally, there was a higher number of preterm births compared to full-term births among the patients included. Interestingly, nearly all patients with cervical stenosis that achieved pregnancy experienced premature labor. At first glance, this appears to contradict the theory that a stenosed cervix would be more resistant to early dilation. However, this apparent paradox can be explained by the underlying structural and functional changes associated with stenosis. Although the cervix may appear anatomically narrow, these alterations can compromise its flexibility and biomechanical integrity during pregnancy, thereby increasing the risk of functional cervical insufficiency[38]. In fact, studies show that cervical changes, regardless of their etiology - including surgical interventions, infections or congenital alterations - can compromise the functional integrity of the cervix, favouring the occurrence of cervical insufficiency[37]. Notwithstanding, among the pregnant patients in this cohort, preterm birth was directly associated with a cervical factor in only two cases: one involved a diagnosis of short cervix at 32 weeks of gestation, while the other corresponded to a case of cervical insufficiency. These findings suggest that, although cervical pathology may contribute to preterm birth in select cases, it was not the predominant factor in most instances within this population.

The mean duration of hospitalization observed in this study was notably prolonged. However, this finding was predominantly influenced by two outlier cases—one patient with an admission lasting 67 days and another with a 23-day hospitalization. These atypically prolonged stays, which occurred mainly during pregnancy, disproportionately affected the overall mean, and their exclusion would markedly reduce the average length of hospital stay.

The main limitations of this study were the small sample size and the presence of multiple concurrent infertility factors among participants: 21 out of the 24 patients presented with additional concomitant causes of infertility, such as ovulatory, tubal, or male factors. This high prevalence of multifactorial infertility complicates the ability to isolate the specific impact of cervical pathology on the observed fertility treatments and obstetric outcomes. This also precluded the possibility of performing a robust statistical analysis. In the future, a study with a larger sample of women and a sole emphasis on instances with cervical pathology would be intriguing to carry out. With this method, the target population may be analyzed more thoroughly and precisely, allowing for more thorough data collection and the drawing of statistically significant conclusions. Additionally, the variability caused by other factors is removed by limiting the study to women with cervical abnormalities only, leading to more accurate results that can be used in clinical practice.

Furthermore, the new 2024 guidelines recommending initiation of cervical cancer screening only at the age of 30 may delay the diagnosis of cervical pathology, potentially necessitating the use of more invasive diagnostic and therapeutic techniques that compromise the anatomy and functionality of the cervix. Such delays could adversely affect cervical integrity, with possible implications for fertility. Therefore, it is imperative to direct greater investigative efforts toward understanding the influence of cervical factors on female fertility to provide effective management and support for these patients in the future.

5. Appendix

Table I - Patients' features.

	Total (*N* = 25)				
	n	*%*	*M*	*Standard Deviation*	*Range*
Age (years)	25		35.36	3.226	11
BMI (Kg/m^2)	25		24.19	4.19	16.0
Pregnancy			0.64	0.995	3
0	16	64			
1	4	16			
2	3	12			
3	2	8			
Parity			0.16	0.374	1
Nulliparous	21	84			
Nonnulliparous	4	16			
Infertility Time (years)	25		4.14	1.64	6.5

Table III - Infertility factors.

	Total (*N* = 25)	
	n	*%*
Male Infertility	6	24
Ovulatory Infertility	10	40
Uterine Infertility	7	28
Cervical Infertility	25	100
Tubarian Infertility	2	8
Thyroid Disease	5	16
Other	2	8

Table III - Infertility factors: Cervical factors.

	Total (*N* = 25)	
	***No*. patients**	***%***
Anatomical defects	22	*88*
Stenosis	19	*76*
Iatrogenic (diagnostic and therapeutic procedures)	9	*36*
CIN medical history	7	*28*
CCU medical history	2	*8*
Adenomyosis	6	*24*
Idiopatic	4	*16*
Cervical Neurofibroma	1	*4*
Incomplete septated uterine cérvix	1	*4*
Short cervical length - Trachelectomy	1	*4*
Others (probable mucus abnormality due to thyroid disease)	3	*12*

Table IV - Assisted reproductive techniques and pregnancy outcomes.

	Total (N=25)				
	n	*%*	*M*	*Standard Deviation*	*Range*
No. attempts	25		3.56	1.76	6
Infertility factors and outcomes					
With uterine pathology	7	*28*			
Pregnancy	2	*8*			
No pregnancy	5	*20*			
Without uterine pathology	18	*72*			
Pregnancy	12	*48*			
No pregnancy	6	*24*			
Latest Fertility treatment technique used and outcomes					
AI	4	*16*			
Pregnancy	3	*12*			
No pregnancy	1	*4*			
IVF	11	*44*			
Pregnancy	7	*28*			
No pregnancy	4	*16*			
ICSI	10	*40*			
Pregnancy	4	*16*			
No pregnancy	4	*16*			
Cancelled	2	*8*			

Table V - Pregnancy complications.

	Total (n=11)	
	n	*%*
First trimester spontaneous abortion	1	*9*
Placenta previa	2	*18*
Preterm premature rupture of membranes	2	*18*
Intrauterine growth restriction	2	*18*
Short Cervical Length	1	*9*
Preeclampsia	1	*9*
First trimester bleeding	7	*64*

Table VI - Relation between cervical pathology and pregnancy weeks at labor.

	Total (*N* = 10)	
	No. patients Pre-term Labor	*No. patients Full-Term Labor*
Anatomical defects		
Stenosis		
Iatrogenic (diagnostic and therapeutic procedures)	4	
CIN medical history	3	
CCU medical history	1	
Adenomyosis	1	
Idiopatic	1	1
Cervical Neurofibroma		1
Incomplete septated uterine cervix		1
Short cervical lenght - Trachelectomy		
Others (probable mucus abnormality due to thyroid disease)		1
Total	6	4

Table VII - Number of days of hospitalization, and types of delivery.

	Total (n)=10				
	n	**%**	**M**	**Standard Deviation**	**Range**
Number of days hospitalized	10		13.50	19.962	64
Eutocic delivery	2	20			
Instrumental delivery	0	0			
Scheduled cesarean section	3	30			
Placenta previa	2	20			
Fetal growth restriction	1	10			
Urgent cesarean section	5	50			
PPROM at 34 weeks	2	20			
Chorioamnionitis	1	10			
Arrested active phase	2	20			

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