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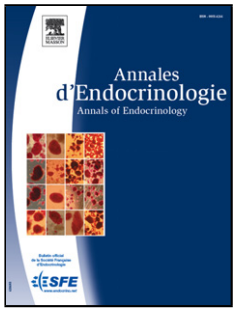

Sertoli cell-only syndrome (Del Castillo syndrome): Past, Present and Future

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Sertoli cell-only syndrome (Del Castillo syndrome): Past, Present and Future

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Abstract

Del Castillo, Trabucco and De la Balze syndrome was described in five patients in Buenos Aires in 1947. Secondary sexual characteristics and urological examination were normal, except for small testicle volume ("the size of an olive"). Treatment with hCG was ineffective. On testicular biopsy, only Sertoli cells and seminiferous tubules were detected, with no spermatozoa or spermatogonia. For this reason, it is currently known as testicular germ-cell aplasia or Sertoli cell-only syndrome (SCOS). SCOS is the most severe histological phenotype of male infertility, associated with non-obstructive azoospermia and low testicular volume. This review provides a comprehensive synthesis of the historical background, clinical presentation, hormonal and histological features, genetic underpinnings and emerging therapeutic perspectives in SCOS.

Key-words: Del Castillo, germinal aplasia, Sertoli cell-only syndrome, infertility, gonads

Introduction

In 1945, an Argentinian urologist, Dr. Armando E. Trabucco (1902-1984) described four patients with no history of infection or trauma, suffering from non-obstructive azoospermia **(1).** Secondary sexual characteristics and urological examination were normal, except for small testicle volume ("the size of an olive"). Treatment with hCG was ineffective in restoring spermatogenesis. On testicular biopsy, only Sertoli cells and seminiferous tubules were detected, empty of spermatozoa and spermatogonia (**Figure 1**). Trabucco interpreted this picture as "congenital germline aplasia". He postulated, like in other animal models, that it resulted from the absence of migration of primary gonocytes into the testes during embryogenesis **(1-3).**

In 1947 in Buenos Aires, Dr. Trabucco, in collaboration with two endocrinologists, Dr. Enrique Benjamin Del Castillo (1897-1969) and Dr. Felipe De la Balze (1910-2009) communicated the hormonal and anatomopathological aspects of this new syndrome in the publication: "Syndrome produced by absence of the germinal epithelium without impairment of the Sertoli or Leydig cells" **(4).** The authors measured the urinary bioactivity of FSH and the 17 ketosteroids in five azoospermic patients. FSH values were normal while ketosteroid values were slightly subnormal (LH and testosterone levels were not yet available at that time, the authors noted).

De la Balze, who assisted Professor Albright's department at the end of the Second World War, was well acquainted with the Klinefelter, Refestein and Albright syndrome, described in Baltimore in 1942 **(5)** in nine men with gynecomastia and eunuchoidism, low testicular volume, elevated FSH and decreased ketosteroids. Del Castillo and Klinefelter syndromes were recognized at that time as two distinct entities. In particular, testicular biopsy in Klinefelter syndrome usually demonstrates variable destruction of germ cells, seminiferous tubules, with the presence of Sertoli and Leydig cells **(5-8).** While an XXY karyotype is systematically found in Klinefelter syndrome, the different causes responsible for Del Castillo syndrome have yet to be elucidated (**5-8**).

Today, Sertoli cell-only syndrome (SCOS) is the most severe histological phenotype of male infertility: it is characterized by the absence of germ cells, with only Sertoli cells in the seminiferous tubules, as initially described by Del Castillo et al.. SCOS affects 26.3% to 57.8% of men with azoospermia (**5-8**). Patients with SCOS therefore cannot naturally father children **(5-8).**

In this article we synthesize the available clinical, biological and genetic data as well as the most recent perspectives on the treatment of this condition.

Review criteria and research strategy

The causes of non-obstructive azoospermia (NOA) can be pretesticular (for instance, Kallmann syndrome) or testicular (**5-10**). This review focuses on testicular causes. While NOA is a clinical diagnosis, SCOS is a histological diagnosis and a subset of NOA. For the review, we focused on SCOS studies whenever as possible.

An extensive search on PubMed was conducted for the period 1958 to 2025, using the following key-words: ('SCOS' [MeSH Terms]) OR ('Sertoli cell only syndrome' [MeSH Terms]) OR ('Del Castillo syndrome'[All Fields]). The search was limited to articles in English, involving humans (174 articles). We retrieved 122 articles: 70 original papers, 6 meta-analyses, 32 narrative reviews and 14 systematic reviews. The reference lists were searched manually to find additional references. We finally included 62 references. For the section on SCOS treatment, the main reviews and meta-analyses on sperm

extraction and the following causes of NOA were retrieved: Klinefelter syndrome, ectopic testis, idiopathic NOA, and azoospermia factor C (AZFc) microdeletion. The following information was extracted: author, year of publication, sample size, total sperm retrieval rate (SRR), pregnancy rate and live birth rate. The complete search is summarized in **Table 2**.

SCOS: Diagnosis and clinical management

Azoospermia is present in 10–15% of males consulting for infertility (**5-10**). It should be confirmed in at least two semen specimens **(7-9**). History, physical examination and hormonal analysis can distinguish non-obstructive from obstructive azoospermia (**6-10**). Normal or elevated gonadotrophins indicate a testicular cause of NOA (**6-10).** Testicular biopsy with histopathologic examination is the gold-standard diagnostic test for SCOS, distinguishing between other NOA subtypes such as hypospermatogenesis, maturation arrest, tubular sclerosis and mixed patterns (**8-12**).

Except in Klinefelter syndrome (**5,8,12**), clinical examination of SCOS patients reveals normal secondary male sexual characteristics, and no gynecomastia is seen. As summarized in **Table 1**, testes volume may be normal or small. Luteinizing hormone (LH) and testosterone (T) secretion are usually in the normal range. Serum T concentrations in males with NOA may range from low to normal. In some cases, a compensatory rise in LH may occur to maintain adequate T secretion by Leydig cells (**6,8).**

Inhibin B, secreted by Sertoli cells, regulates pituitary FSH secretion through negative feedback (**7,8**). Decreased Sertoli cell function reduces inhibin B secretion. Thickening of the seminiferous tubule walls may impair hormonal permeability and influence inhibin B levels in the peripheral blood (**8, 9**).

Testicular ultrasound is useful for assessing testicular volume and identifying microlithiasis or tumoral lesions (**13**). Testicular microlithiasis is defined by five or more hyperechoic lesions, each smaller than 3 mm in diameter, without acoustic shadowing, and diffuse in nature (**13**). Barda et al. observed that, in 16 out of 110 men with NOA (14.5%), the prevalence of microlithiasis correlated with histopathology (**14**). Histologically, microliths (also known as calcospherites) are mainly found in the seminiferous tubules and are spherical or elongated and eosinophilic in nature. Microliths comprise two zones: a central calcified zone and a multilayered envelope of stratified collagen fibers (**13-15**).

Microlithiasis is a marker of risk of malignancy, as testicular germ cell tumors have been reported in 6-46% of such cases (**13-15**). The prevalence of testicular tumors in men with SCOS is non-negligible (**16,17**). Recent guidelines recommend testicular ultrasound screening in azoospermic patients coupled with testicular histological analysis in the context of assisted reproductive technology (**15-17**).

Routine genetic tests recommended in NOA include cytogenetic karyotyping, Y-chromosome microdeletion subtyping and molecular diagnostics (**7-9**). Although most men with SCOS have a normal karyotype, SCOS may result from Klinefelter syndrome or Y-chromosome microdeletions (**7-9**). Additional genetic causes are discussed in the following section and summarized in **Table 3**. Sperm retrieval followed by intracytoplasmic sperm injection (ICSI) is one treatment option for SCOS (**6-10**). As well as issues of fertility, testicular nodules and cancer are prevalent in men with complete SCOS (**16,17**), warranting clinical and endocrine follow-up, although definite guidelines are lacking (**see sperm retrieval section**).

SCOS and Testis Embryogenesis

The first microscopic studies in human embryos by Politzer and Witschi (**2,3**) demonstrated migration of germ cells from the yolk sac to the primitive gonadal folds (**3)**. From mouse models (**18**), it is known that, during embryogenesis, primordial germ cells (PGSs), located in the posterior endoderm, proliferate. They then move to the dorsal mesentery and migrate to the genital crest. The majority of PGCs colonize the genital crest and continue to proliferate, then enter mitotic quiescence and gradually differentiate into gonocytes (**3,19**).

Sertoli cells are the first type of viable somatic cells in the primitive testis (**3,19**). They initiate and maintain testicular differentiation, while blocking differentiation into ovaries (**19**). Sertoli cells coordinate the differentiation of all other cell types within the testis, including germ cells (**3,19**). Anti-Müllerian hormone (AMH) is secreted by fetal Sertoli cells from the 7th week of gestation (**19, 20**). During embryogenesis, AMH, secreted at a high rate, causes regression of the Müllerian ducts, allowing clear differentiation of male sex (**3,19**). At birth, AMH levels remain high until puberty, helping to maintain a testicular environment conducive to spermatogenesis (**19, 20**). In male adulthood, AMH concentrations are low but detectable. AMH can be used as an indirect marker of Sertoli cell function (**20**).

Only Sertoli cells express the FSH receptor (FSHR) (**19, 20**). Androgens derived from fetal Leydig cells are responsible for the maintenance of Wolff's ducts and their subsequent development into male accessory sex glands and urogenital structures (**3, 19, and 20**). AMH is also involved in promoting the transition of germ cells from gonocytes to spermatogonia (**3, 19, and 20**).

While a single layer of mioid cells encapsulates the seminiferous tubules of rodents, the sheet of peritubular cells in humans, called the lamina propria, is thick, comprising five to seven layers and intertwined mioid cells (**19,21**). In addition to mioid cells, fibroblasts are also incorporated into the human lamina propria (**21**). Impaired spermatogenesis is often associated with thickening of the lamina propria (**21)**.

Leydig cells are dependent on Sertoli cell interactions (**18**). Pre-Sertoli cells are recruited directly, by high *SRY* gene expression, or indirectly, via secreted factors (**3,18,19**). Minipuberty, characterized by an increase in sex gonadotropin and steroid levels, occurs shortly after birth (at the age of ∼1 to 4/6 months): it is the final stage in the differentiation of gonocytes into infantile spermatogonia (**3-19**). The blood-testis barrier is established at puberty by the tight junction of Sertoli cells, forming basal and apical compartments within the seminiferous epithelium (**21**). Germ cells reside in the apical compartment and are protected from the immune system and blood-borne toxins (**3,19**). As discussed below, in patients with SCOS, Sertoli cells fail to provide adequate support for germ cell survival or differentiation (**18-21**).

SCOS: Histopathology, SCOS variants and mosaicism

Testicular biopsy in SCOS typically shows seminiferous tubules lined only by Sertoli and Leydig cells, with complete absence of germ cells, leading to NOA (**1,2,11,22**). Interestingly, on testicular biopsy or testicular sperm extraction (TESE) analysis, many SCOS patients have focal areas of active

spermatogenesis (**7, 11,22**), suggesting that SCOS may not be a uniform histological condition across the entire testis (**11,22**).

Importantly, Sertoli dysfunction is suspected in SCOS (**22**). Compared to normal testes, SCOS Sertoli cells exhibit differential expression of genes involved in metabolic support, phagocytosis and structural integrity (**22-24**). Variations in gene expression, chromosomal abnormalities and even local differences in endocrine or paracrine signaling may preserve germ cells in specific niches (**23,24**).

For instance, although most testicular tissue in Klinefelter syndrome shows hyalinized seminiferous tubules and SCOS-like histology (**25**), patches of seminiferous tubules with ongoing spermatogenesis have been identified. Some testicular cells may carry a normal 46,XY karyotype amidst the predominant 47,XXY population (**23-25**). Recent data suggest that micro-mosaic loss of the additional X-chromosome is needed for Sertoli cells to mature and to allow focal spermatogenesis. (**24**)

Usually, a histological distinction is made between focal and generalized SCOS (**23, 24**). Focal SCOS is characterized by residual areas of normal spermatogenesis within the testicle (**23**), whereas generalized SCOS involves absence of germ cells in all biopsies (**23**) (**Figure 1**). Ultrastructural analysis by transmission electron microscopy, however, can identify a small number of germ cells that are not otherwise detected in light microscopy. In addition, electron microscopy of Leydig cells objectifies the endoplasmic reticulum, mitochondria and intracellular lipid droplets, useful clues of testosterone synthesis (**23-24**).

There are two distinct pathophysiological models of SCOS (**21-23**). In primary SCOS (or congenital type germline aplasia), which is less common, Sertoli cells have a fetal appearance with cylindrical cytoplasm and round nuclei (**22-24**). The empty tubules do not show thickening of the tubular wall or the inner collagen layers. In secondary SCOS, Sertoli cells exhibit cytological features similar to those of post-pubertal testes, with irregularly shaped nuclei and diffuse cytoplasmic distribution of vimentin (**22-24**); the seminiferous tubules are small in diameter, with hyalinization and thickening of the tubular wall and peritubular fibrosis (**22-24**).

Thickening of the seminiferous tubule wall can alter the relationship between Sertoli cells and interstitial tissue and thus may affect hormone permeability (**21**). This can inhibin B and FSH secretion in the peripheral blood (**21, 23).**

Primary SCOS, which aligns with the entity originally described by Del Castillo et al. (2), is believed to result from prenatal abnormalities in primordial germ cell development or migration, leading to congenital absence of germ cells.

Secondary or mixed SCOS arises from germ cell loss after initial establishment and may be related to genetic, hormonal, toxic, or inflammatory conditions, including Klinefelter syndrome. In both non-mosaic and mosaic Klinefelter syndrome, germ cell depletion begins early but progresses largely postnatally, particularly at puberty. Mosaicism contributes to intratesticular heterogeneity, allowing for focal preservation of spermatogenesis in some seminiferous tubules despite widespread Sertoli cell–only changes elsewhere. (**23-25**).

Etiology of SCOS

SCOS is a histologic phenotype rather than a single disease entity, and can result from genetic or acquired causes (**23, 24**), although etiology is idiopathic in up of 70% of men with non-obstructive azoospermia (iNOA) (**16**). Known causes comprise genetic abnormalities (**see Genetics section below**), including Y chromosome microdeletion (AZFc), XXY karyotype (Klinefelter syndrome) and autosomal chromosomal abnormalities, testicular damage induced by cytotoxic chemotherapy or radiotherapy, viral infection, exposure to a harmful occupational environment (**26-33**), and testicular abnormalities such as cryptorchidism or ambiguous genitalia (**33**). Auto-immune mechanisms have also been implicated in a subset of SCOS cases (**27**). Auto-antibodies against sperm and testicular proteins were detected in some patients, suggesting a breakdown of tolerance mechanisms (**27**). **Table 2** shows a detailed summary of etiologies and pathophysiological mechanisms**.**

SCOS: Genetics

Genetic causes of SCOS can involve a variety of mechanisms: early embryonic arrest, cryptorchidism, hormonal dysregulation, or direct spermatogenic failure. However, many genetic contributors to SCOS are unidentified or poorly characterized (**29-34**).

The most frequently observed chromosomal abnormality associated with SCOS is Klinefelter syndrome (47,XXY and its mosaic variants), which impairs spermatogenesis via altered gene dosage and hormonal imbalance (**25**). Another well-established genetic cause involves Y chromosome microdeletion in the azoospermia factor (AZF) regions AZFa, AZFb, AZFbc and AZFc, which, taken together, are detected in approximately 13% of men with NOA (**30**). Complete deletion in the AZFa and AZFb regions is associated with SCOS and meiotic arrest (**34, 35**). Notably, deletion of the USP9Y gene (located in AZFa) has been implicated in the disruption of spermatogonial proliferation, a hallmark of SCOS (**35, 36**).

Direct sequencing of candidate genes in unrelated patients with SCOS revealed pathogenic variants in numerous genes: AR, CUL4B, GILZ, CDK2, DMRT1, ETV5, FGF9, H3T, LRWD1, NANOS1, NR5A1, PAPOLB, PLK4, RAD21L, and SEPTIN12 (**30-34**). Among these, AR (androgen receptor), DMRT1 (Doublesex and Mab-3 related transcription factor 1), and NR5A1 (nuclear receptor subfamily 5 group A member 1, encoding steroidogenic factor 1) were repeatedly implicated in azoospermia in independent studies (**30**). Additionally, studies in mouse models confirmed the SCOS phenotype following mutations in GILZ (X-linked gene glucocorticoid-induced leucine zipper), ETV5 (ETS variant transcription factor 5), PLK4 (polo-like kinase 4) and SIN3A (Swi-independent 3).(**30-34**).

Aberrant expression of FGF9 (fibroblast growth factor 9) was associated with SCOS in both humans and mouse models (**32, 37**). In mice, Fgf9 knockout results in a SCO-like phenotype. In humans, a polymorphism (c.-712C/T) in the FGF9 promoter region correlates with decreased gene expression, potentially mediated by altered microRNA activity (**32, 37**).

Cryptorchidism is a major risk factor for male infertility and is frequently associated with SCOS (**38**). Mutations in the INSL3 gene and its receptor LGR8 (also known as GREAT) have been linked to this

condition (**38)**. In syndromic forms such as Prader-Willi syndrome, cryptorchidism is present in 80–100% of male patients, and cases of SCOS have been well documented in this context. (**39**).

Hormonal signaling disruptions may also contribute to SCOS pathogenesis (**19, 33**). Follicle-stimulating hormone (FSH) promotes Sertoli cell proliferation and germ cell support via its receptor (FSHR) (**19, 33**). While complete FSHB gene knockouts in mice may not result in infertility, human mutations or polymorphisms in FSHB and FSHR were associated with spermatogenic failure (**19, 32**). One example is the FSHB-211G>T genotype, found in 25% of men with oligospermia and low FSH, though this variant was not detected in SCOS cohorts (**40**).

Androgen receptor (AR) signaling plays a pivotal role in Sertoli cell maturation and maintenance of the spermatogenic niche (**19, 33**). Mutations in the X-linked AR gene can cause a range of male reproductive disorders (**33**). The CAG repeat length in the AR gene has been studied extensively; one study suggested that the CAG 21 allele may increase the risk of idiopathic SCOS (**41**).

Whole exome sequencing in familial cases and targeted sequencing in sporadic cases uncovered additional candidate genes potentially linked to SCOS (**32, 33**). Transcriptomic, proteomic and epigenetic omics-based approaches have enhanced our understanding of the molecular basis of SCOS (**33**). A summary of these candidate genes is provided in **Table 3.**

Many of the identified genetic variants affect processes critical to meiosis, chromatoid body formation, histone-to-protamine transition, cell cycle regulation, and transcription (**34**). Although knockout mouse models identified hundreds of genes essential for spermatogenesis, only a small subset was directly associated with azoospermia or SCOS in humans (**32, 37**). Greater integration of human genomic data with animal findings is necessary to bridge this gap and improve diagnostics and therapeutic targets for SCOS (**33, 37**).

SCOS: Therapeutic Options

a) Before Testicular Biopsy

In severe varicocele and NOA, surgical repair may be considered (**42**). Elevated intra-testicular temperature associated with varicocele is known to impair spermatogenesis (**43**). While data in SCOS patients are limited, surgery may be beneficial in selected cases, particularly when mosaic histological patterns are suspected (**33, 42, and 43**).

Hormonal stimulation therapy is also under investigation for NOA patients (**44**). Agents such as hCG, FSH, clomiphene citrate or aromatase inhibitors can improve spermatogenesis, particularly in case of hormonal imbalance with low testosterone (**44**). However, in cases of pure SCOS, characterized by complete germ cell aplasia, these therapies have limited efficacy. Paulis et al. reported successful sperm retrieval in a patient with NOA following recombinant FSH therapy, followed by embryo transfer and the birth of a child (**45**). In our own cohort (**46**), hormonal stimulation with clomiphene or a combination of FSH and hCG was administered to 29 men with NOA. Only 3/14 cases had SCOS proven on histology. After hormonal stimulation, sperm production was observed in 6 patients, and 2 live births were achieved (**46**). Further studies are required to establish predictors of response and long-term outcome.

b) Assisted Reproductive Techniques (ART)

Histologic Mosaicism and TESE Rationale

The heterogeneous nature of spermatogenesis in NOA patients was first identified through fine-needle aspiration mapping in 1997 and later with microdissection testicular sperm extraction (mTESE) in 1998 (**46**). Testicular histologic mosaicism refers to the presence of varying spermatogenic patterns within the same testis (**11, 46-48**). In patients with SCOS, this may include focal areas of hypospermatogenesis, particularly in conditions such as Klinefelter syndrome, cryptorchidism and certain genetic syndromes (**11, 46-48)**. This mosaicism underlies the rationale for targeted sperm retrieval techniques such as mTESE (**48, 49**).

Conventional vs. Microdissection TESE

Conventional TESE involves multiple random biopsies through the tunica albuginea, with microscopic examination of removed tubules (**47**). In contrast, mTESE is performed under an operative microscope, enabling the identification of dilated seminiferous tubules likely to harbor active spermatogenesis (**46**). Although more invasive and requiring general anesthesia, mTESE has the potential to yield sperm with minimal tissue excision (**11, 46-48**).

Notably, mTESE is particularly advantageous in SCOS cases with isolated foci of spermatogenesis (**11, 48**). The use of an operative microscope increases the likelihood of identifying such foci while minimizing tissue damage. In these cases, concurrent histopathologic analysis and screening for carcinoma *in situ* may be warranted.(**16**)

Sperm Retrieval Outcomes by Etiology

Sperm retrieval rates (SRRs) vary significantly depending on NOA etiology (**47, 48**). For instance, a systematic review reported SRRs of 86% in incomplete germ cell aplasia and 19.3% in complete SCOS (**48**). Patients with secondary SCOS (e.g., post-chemotherapy or post-infection) generally show better outcomes than those with primary SCOS. (**47- 50**)

A meta-analysis by Corona et al. found higher SRRs in mTESE (57%) than cTESE (39%), although this was not confirmed in the only available randomized controlled trial (**51**). The success of mTESE depends significantly on the underlying diagnosis (**47-55**). For example, patients with idiopathic NOA had a lower SRRs (36.8%) than those with defined causes such as Klinefelter syndrome (43%), AZFc deletion (62%) or cryptorchidism (60%) (**Table 3**). In contrast, AZFa and AZFb deletions are associated with negligible success. (**54**).

Whereas ICSI combined with effective SSR (surgical sperm retrieval), remains a viable option for achieving fertility in patients with NOA, overall success in achieving pregnancy with testicular sperm retrieved from mTESE in NOA patients is inadequately documented (**51**). Pregnancy rates and all live births are also presented in **Table 3**.

Complications and Follow-up

Despite its benefits, TESE, and especially microdissection, can incur complications such as testicular fibrosis, hematoma, and atrophy (**50**). A 20% decline in serum testosterone can be observed within 3-6 months post-procedure. Endocrine follow-up and testosterone replacement therapy should be considered in symptomatic patients (**50**).

Guidelines and Controversies

There is no consensus between major guidelines regarding superiority of mTESE over cTESE (**56**). The AUA, ASRM, and Japanese guidelines support mTESE in NOA patients (**6, 7, 10**), but are based on low-quality evidence (**56, 57**).

During medical evaluation for TESE or micro-TESE, patients should be counseled about the invasive nature of these procedures and the possibility of sperm retrieval failure if spermatogenesis is severely impaired (**6-8**). Lifestyle optimization such as avoiding alcohol, smoking and drugs, following a healthy diet and taking exercise should also be previously discussed (**6-8**). When sperm retrieval is unsuccessful, couples may consider donor sperm insemination or adoption to achieve parenthood (**6-8,32**).

Conclusions and Perspectives

Although hormonal therapy may occasionally induce spermatogenesis in mosaic SCOS (**50**), the likelihood of success remains low in pure forms. Innovative strategies such as in-vitro maturation of induced pluripotent stem cells (iPSCs) derived from testicular tissue are being explored (**59-61**). Abofoul-Azab et al. (**62**) recently demonstrated in-vitro induction of meiotic and post-meiotic cells from germ-cell-free biopsies of SCOS patients, raising the possibility of future fertility restoration.

SCOS is one of the most severe forms of male infertility. While clinical advances such as mTESE have provided hope for some patients, a deeper understanding of the pathophysiology and ongoing translational research are essential to uncover new therapeutic possibilities.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Clinical, hormonal, ultrasound and histological characteristic of SCOS.

Domain	Characteristics
Clinical	Azoospermia, small firm testes, usually normal virilization. Associated syndromes: Klinefelter, Prader-Willi
Hormonal	Normal or ↑ FSH, ↓ Inhibin B, normal or ↑LH, variable testosterone levels
Ultrasound	Small testicular volume (<12 ml), homogeneous echotexture and microlithiasis may be found, normal or ↓ blood flow, increased testicular stiffness with elastography.
Histology	Tubules lined only by Sertoli cells and Leydig cells, with no germ cells; basement membrane thickening is common. There may be focal spermatogenesis in mosaicism. Two forms: **pure SCOS** (entire testis affected) and **focal SCOS** (isolated areas of spermatogenesis, detectable on microdissection TESE).

Table 2: Etiologies of SCOS and their respective pathophysiological mechanisms (**references 6-10**).

Etiology	Pathophysiological Mechanism
Genetic (e.g., Y microdeletion)	Loss of germ cell-specific gene function
Chromosomal (e.g., KS)	Testicular dysgenesis and germ cell apoptosis
Cryptorchidism	Heat-induced germ cell degeneration
Chemotherapy/Radiation	DNA damage and stem cell depletion
Toxins	Oxidative stress and Sertoli/germ cell junction disruption
Infection	Inflammatory destruction and fibrosis
Auto-immunity	Immune-mediated germ cell loss
Idiopathic	Possibly subtle or unknown gene/environment interactions

Figure 1: Right testicular biopsy of Sertoli cell-only syndrome (40 x, hematoxylin eosin). The seminiferous tubules are of regular size, surrounded by sharply thickened membranes (green arrow) and lined with a layer of mature and immature Sertoli cells (yellow arrows). The tubes rest on a fibrous framework, with rare islands of Leydig cells (blue arrow). No germ cells are visible. (Credits: Microphotography: Dr L Coppens, one of the authors, with permission).

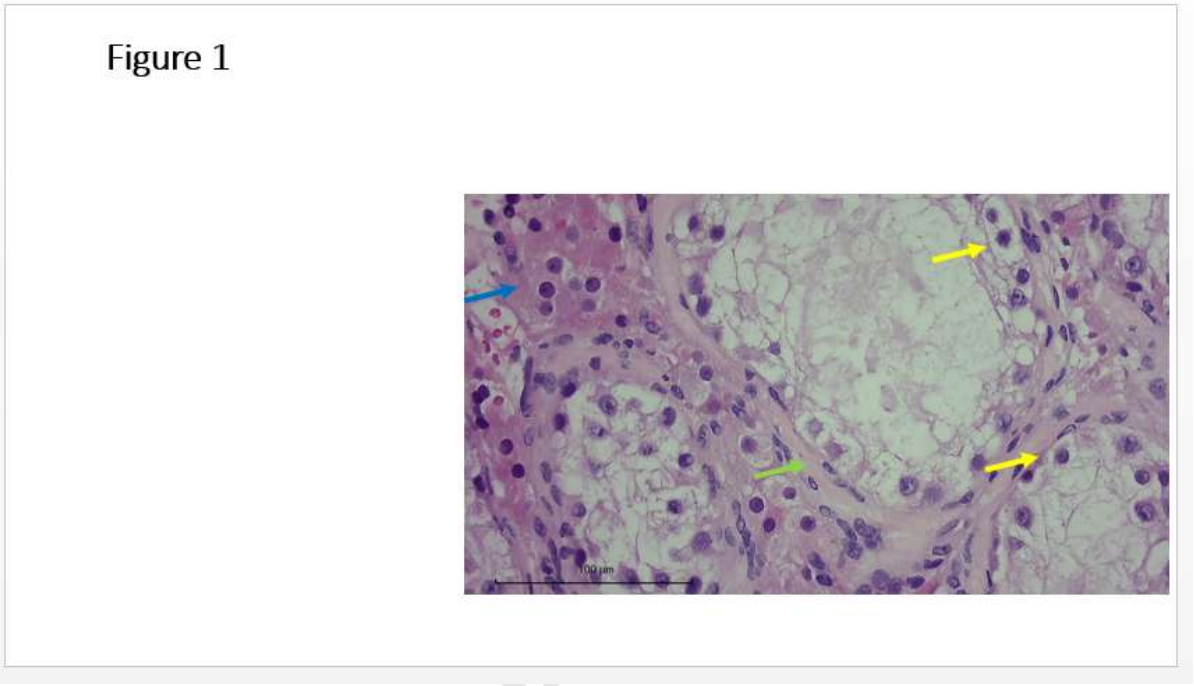

Table 3: Largest series and meta-analyses evaluating TESE/mTESE outcomes with ICSI in men with non-obstructive azoospermia (NOA), focusing on sperm retrieval rates.

Author, Date	Study design	Population	SSR%- cTESE	SSR%- mTESE	Pregnancy Rate %	Live birth rate %
Corona et al. **2019** (51)	Meta-analysis	General NOA 21 404 patients	56 studies:46 (43-49) 7 studies: 57 (47-59)	43 studies:46 (42-49) Q: 0.02, p: 0.88 7 studies: 39 (25-45) Q: 9.17, p: 0.002	N: 1,096 cases all:29% (25-32) 7 studies: na	N:569 cases all: 24% (20-28) 7 studies: na
Corona et al. **2017** (58)	Meta-analysis	Klinefelter 37 studies 1,248 patients	studies:43 (35-50)	studies: 45 (38-52) Q:0.2, p:0.65	N:218 cases All: 43% (36-50)	N:211 cases All: 43(36-53%)
Qin ZH et al. **2024** (63)	Meta-analysis	Cryptorchidism 1,496 patients	6 studies, 1 mixed All:60 (54-66)	14 studies,1 mixed All: 59 (52-67) p: 0.874	14 studies, all: 315 cases 37.6 % (36-50)	14 studies, all: 264 cases 32 % (24-40)

Jiao ZY et al. **2024** (54)	Meta-analysis	Factor c microdeletion 11 studies 711 patients	na	441 patients 62% (25-85)	20.4% (12-23)	11.9% (2-18)
Xiao et al. **2024** (20)	Meta-analysis	Idiopathic NOA 1,892 patients	na	9 studies 36.8 (27-46%)	na	na

General NOA: patients including all main NOA causes. Pregnancy rate: biochemical pregnancy/ICSI, na: not available or very few data to analyze

Table 4: Gene mutations identified in NOA patients. (32,33)

Meiosis	**Chromatoid body function**	**Cell Cycle**	**Histone-to-protamine exchange**	**Enzymatic activity**	**Transcription factor**
SYCP3	TDRD9	CDC20	HIWI	USP26	GTF2H3
SYCE1	TDRD6	HAUS7	PRM1	DDX25	WT1
MEIOB	TDRD7	PLK4	PRM3		E2F1
DMC1		SIN3A			TAF4B
XRCC2					ZMYND15
MEI1					TAF7L
TEX11					NANOS1
TEX15					HSF2
PSMC3IP					ETV5
HFM1					NR5A1
STX2					HOXD9
RNF212					
STAG3					
FKBP6					

Meiosis genes: **SYCP3:** Synaptonemal complex, protein 212; **STAG3**: Stromal antigen 3; **FKBP6:** FKBP Prolyl Isomerase Family Member 6.

Chromatoid body function genes: **TDRD9:** Tudor domain containing 9; **TDRD6:** Tudor domain containing 6; TDRD7: Tudor domain containing 7.

Cell Cycle: **CDC20:** Cell Division Cycle 20; **HAUS7**: augmin-like complex subunit 7; **Histone-to-protamine exchange genes: HIWI:** P-element Induced WImpy testis; **PRM1:** Protamine 1; **PRM3:** Protamine 3; **PLK4:** polo-like kinase 4. **SIN3A** (Swi-independent3)

Enzymatic activity: **USP26:** Ubiquitin Specific Peptidase 2; **DDX25:** DEAD-box helicase 25**.**

Transcription factor: **GTF2H3:** general transcription factor IIH; **WT1:** Wilms tumor protein 1; **E2F1:** E2F Transcription Factor 1; **TAF4B:** Transcription initiation factor TFIID subunit 4B; **ZMYND15**: Zinc Finger MYND-Type Containing 15; **TAF7L**: TATA-Box Binding Protein Associated Factor 7-Like; **NANOS1:** Nanos C2HC-Type Zinc Finger 1; **HSF2**: Heat Shock Transcription Factor 2; **ETV5**: ETS variant transcription factor 5; **NR5A1**: Nuclear receptor subfamily gene encoding the steroidogenic factor 1 (SF-1) protein; **HOXD9:** Homeobox protein Hox-D9.

Table 5: Possible therapeutic approachs for SCOS (57-61).

Treatment	Potential Benefit	Limitations
Micro-TESE + ICSI	Possible sperm retrieval and fertilization	Low success rate in pure SCOS; invasive
Hormonal therapy	May improve sperm production in partial SCOS	Limited efficacy in complete SCOS
Stem cell therapy	Potential future cure	Experimental; not widely available
Donor sperm/adoption	Enables parenthood	Not biological offspring