Journal of Assisted Reproduction and Genetics (2021) 38:559–572
https://doi.org/10.1007/s10815-021-02063-x

REVIEW

Sertoli cell-only syndrome: etiology and clinical management

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Received: 22 September 2020 / Accepted: 2 January 2021 / Published online: 11 January 2021

Abstract

Almost 50% of infertility cases are due to male factors, and spermatogenesis failure is one of the most severe forms of male infertility. Sertoli cell-only syndrome (SCOS) also known as germ cell aplasia is characterized by azoospermia in which the seminiferous tubules of testicular biopsy are lined only with Sertoli cells. The definitive diagnosis of SCOS is by diagnostic testicular biopsy. Although SCOS may be a result of Klinefelter syndrome, most of the SCOS men have a normal karyotype. Along with genetic aberrations, signaling pathways and endocrine processes might be major factors in the development of SCOS. Sperm retrieval and intracytoplasmic sperm injection (ICSI) are available treatments for SCOS. However, some SCOS patients do not have therapeutic options to help them having a biological child. This review aims to summarize our present knowledge about SCOS and to highlight the importance of future researches in the diagnosis and treatment of this disorder.

Keywords Sertoli cell only syndrome · SCOS · Germ cell aplasia · Azoospermia · Male infertility

Introduction

Infertility is considered a major public health issue of recent decades and affects about 15% of couples trying to conceive [1]. Approximately 50% of infertility cases are caused by a male factor [2], that often caused by spermatogenesis failures, problems related to sperm quality (e.g., morphology and/ or motility), and a reduced number of spermatozoa in the semen. Azoospermia, the complete absence of sperm in the ejaculate, is a more severe form of male infertility occurring in 10–15% of males seeking medical care for infertility [3]. Azoospermia can be classified as obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). OA results from any obstruction along the male reproductive tract that prevents spermatozoa to reach the ejaculate, while NOA is characterized by severely impaired spermatogenesis due to endogenous or exogenous abnormalities. Based on histological evaluation of the testicular biopsy, NOA is classified into hypospermatogenesis (HS), maturation arrest (MA), and SCOS [4]. The prevalence of SCOS in azoospermic patients has been reported about 26.3–57.8% [5, 6]. There are various etiologies of human SCOS, which include Y chromosome microdeletions, chromosome disorders, undescended testis, radiation, cytotoxic drugs, and virus infection [7]. However, the causes of it have not been fully understood. SCOS is also known as germ cell aplasia and Del Castillo syndrome, which is characterized by azoospermia in which the seminiferous tubules of testicular biopsy samples are lined only with Sertoli cells. According to the initial description by Del Castillo in 1947, SCOS was characterized by the total absence of germ cells, Sertoli cells with a normal cytoplasm within seminiferous tubules, lack of histological degeneration in the testes, and reduced testicular volume with normal secondary sexual characteristics. The focal and complete SCOS is the two types of this disorder. The focal SCOS is characterized by residual areas of normal spermatogenesis within the testis. On the other hand, complete SCOS is identified with gonocytes that lose their way during migration to the embryonic gonads and non-formation of their germinal epithelium [8]. In the focal SCOS, spermatozoa could be retrieved from the testis by surgical procedures. By harvesting a single, viable sperm from the testis, in combination with ICSI, men with SCOS had this opportunity to father their genetically own offspring [9]. In this review, we present the research findings, including histopathology, genetics,

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epigenetics, signaling pathways, and endocrinology of SCOS, and focus on clinical management. The study of the molecular causes of SCOS has increased greatly in the past decade, enabling understanding of the pathophysiological mechanisms underlying the features of the disorder. This review aimed to provide an overview of the current knowledge regarding SCOS etiology and emphasize the need for future investigation for the management of this disorder.

Methods

PubMed and Google Scholar databases were systematically searched for peer-reviewed original articles identified by relevant keywords, such as "Sertoli cell only syndrome," "SCOS," "SCO," "germ cell aplasia," and "Del Castillo syndrome." Keywords were used in multiple combinations to identify those papers relevant to the Sertoli cell-only syndrome. Further articles were identified by the exact analysis of reference lists from relevant publications. The non-English language articles were excluded, and only original articles published in English that were available online until the end of April 2020 were included in the search. The most relevant publications, for example, those concerning the molecular genetic basis of SCOS were assessed and discussed critically to offer a conclusion for the etiology of the disease. In total, 824 studies were identified through database searching following the search for the keywords. Titles and abstracts from the electronic databases were evaluated, and after full-text papers screening, 155 articles were included in the review. Concerning animal studies, priority was given to publications relevant to the human.

Histopathology

Histological diagnosis of SCOS is confirmed when the examined testicular biopsy sample reveals that all seminiferous tubules are lined by only Sertoli cells, without any germ cells. Because of the testicular tissue heterogeneity, observation of SCO histological pattern in one or more biopsies does not disprove the fact that focal spermatogenesis may exist in a different location within the testis [10]. Two distinct histological patterns of SCO were introduced: primary and secondary SCO [11]. The primary, congenital, or pure SCO is caused by a prenatal defect in the migration of gonocytes into the male gonads, resulting in sterility. On the other hand, secondary or mixed SCO occurs as a result of postnatal damage to the healthy testes that may result in a focal SCO pattern in testicular tissue. The difference between primary and secondary SCO based on the histological evaluation, include histology of seminiferous tubules walls, morphology and function of Sertoli cells, and the interstitial tissue appearance [10, 12]. In primary SCO, the diameter of seminiferous tubules was narrower than normal, with no thickening of the tubular wall, and no thickening of inner collagen layers was observed. Sertoli cells had ovoid or round nuclei with a regular outline and columnar cytoplasm that vimentin distributes in subnuclear basal areas similar to fetal Sertoli cells. On the contrary, in the secondary SCO, seminiferous tubules were small in diameter, tubular wall hyalinization and thickening with peritubular fibrosis, and irregular thickening of the inner collagen layer was observed. Normal Sertoli cells had cytological features similar to post-pubertal testis with irregularly shaped nuclei and diffuse cytoplasmic distribution of vimentin. In some tubules, germ cells were observed [11]. The thickened tubular wall of the seminiferous tubules may impair the relationship between the Sertoli cells population and the interstitial tissue and consequently, affect hormone permeability. This phenomenon may affect inhibin B and follicle-stimulating factor (FSH) levels in the peripheral blood [13]. The lipid content of Sertoli cells is different in two types of SCOS. There are many lipid granules in Sertoli cells cytoplasm of mixed SCOS form due to reabsorption of degenerated germ cells. However, pure SCOS contains a very small amount of lipid and glycogen [10].

It has been reported that four types of Sertoli cells exist in testicular biopsies of SCO tubules that can be identified with light and electron microscopy: (i) normal mature cells with an intended nucleus, triangular shape and with a prominent tripartite nucleolus, (ii) immature cells showing round regularly outlined nuclei and immature cytoplasm, which formed a pseudostratified epithelium similar to those of prepubertal testes (iii) dysgenetic cells with immature nuclei and almost mature cytoplasm with less-developed cytoplasmic organelles and (iv) involuting cells with very irregular outlined nuclei and a mature cytoplasm showing characteristic organelles of the normal mature Sertoli cells and atypical inter-Sertoli junctional specializations [12]. The state of differentiation of Sertoli cells can be determined by the presence or absence of Sertoli cell-specific maturation markers [14, 15].

Ooba et al. (2008) reported that the basement membrane thickness in patients with SCO was significantly greater and testicular tubule diameter was smaller than in those with OA. Besides, in patients with SCO, expression of an extracellular matrix component, laminin, was increased and an overabundance of laminin-specific chains in seminiferous tubules may result from inhibition of spermatogenesis. They also showed a significant decrease of seminal laminin in the SCO patients, so assessing seminal laminin levels could lead to the prediction of the SCO pathology in the infertile men [16].

Endocrinology

Abnormalities in the paracrine regulation of spermatogenesis may contribute to the SCOS pathophysiology. However, it has

been reported a unique case of SCOS with normal gonadotropins [17]. Also, it has been reported a significant decrease in serum estrone, estradiol, progesterone, 17a-hydroxyprogesterone, and dihydrotestosterone, and a significant increase in serum estriol and testosterone (T) in men with SCOS [18]. A selective increase in FSH levels has been reported in SCOS [19]. FSH stimulates inhibin B secretion by Sertoli cells. This process also is modulated by interactions between Sertoli and germ cells [20]. It has been reported that in SCOS patients basal FSH serum levels were higher, and basal luteinizing hormone (LH) concentration was similar to normal adult males [21]. Endocrinological abnormalities in patients with SCOS were mild compared to those in patients with Klinefelter syndrome. Elevated levels of serum LH, as well as FSH and lowered levels of serum testosterone, suggested Leydig and germ cell failure [22]. In another study, the serum FSH and LH levels in patients with SCOS were significantly higher than in normal males. The elevated basal serum LH levels and normal serum testosterone levels indicated that there was a dysfunction in the Leydig cells in SCOS [23]. It has been reported that all SCOS patients presented with elevated serum FSH levels suggesting Sertoli dysfunction or reduced production of inhibin due to the absence of germ cells [24]. The hormonal profile of SCOS patients has been investigated. Elevated FSH level and decreased Inhibin B levels were observed in SCOS patients. The decrease in the number of functioning Sertoli cells and a large percentage of ghost tubules in SCO can explain the low level of Inhibin B. On the other hand, a thickened tubular wall of the seminiferous tubules probably impairs hormone permeability and levels in the peripheral blood [13].

It has been demonstrated that spermatogenic failure observed in SCOS patients cannot be explained by a change in FSH bioactivity or FSHR mutations [25]. Testicular FSH and hCG receptors were measured in SCOS patients. FSH receptors were found in only 4 of 10 SCOS patients, and human chorionic gonadotrophin (hCG) receptors were detected in all patients with SCOS. The serum levels of LH and FSH in the SCOS group were higher than those in the control group, the level of testosterone in the SCOS group was lower than the control group [26]. Androgen receptor (AR) immunoexpression in Sertoli and Leydig cells of SCOS was higher than spermatogenesis arrest and normal testis samples. This result was associated with the lack of germ cells in the testis and suggested that germ cells had a regulatory effect on AR expression [27]. It has been concluded that the progesterone receptor (PR) and estrogen receptor α (ERα) may play a role in the pathogenesis of the MA and SCO phenotype in infertile men. The expression of PR was reduced in all cell types, and only truncated isoform of PR (52 KDa) was expressed in SCO as compared with that in the OA patients. The expression of ERα was enhanced in the Leydig cells of the SCO testes [28].

Leydig cell dysfunction was found in patients with SCOS that may be due to a disturbing influence from the damaged tubules. 17α-hydroxylation was significantly lower, and the production of 20α-dihydroprogesterone was significantly higher compared to the control group [29]. Altered intratesticular estradiol/testosterone ratio in some patients with complete SCOS suggests that P450-aromatase encoded by *CYP19* is increased and might contribute to Leydig cell impairment [30]. Increased expression of aromatase in Leydig cells leads to higher E2 production and may account for the Leydig cell dysfunction in patients with SCOS [31].

An unusual case of insulinoma was reported that his testicular biopsy showed SCOS. This report emphasized clinicians' attention to the possibility of an association between insulinoma and primary testicular failure [32]. Schematic representation of the hormone levels alternation in SCOS is presented in Fig. 1.

Etiology

Even though SCOS was first described in 1947, its exact etiology remains enigmatic in some cases. SCOS may be a result of Klinefelter syndrome but most of the SCOS men have a normal karyotype, and some have smaller testis and higher levels of FSH [33, 34]. Along with genetic aberrations, signaling pathways and endocrine processes might be major factors in the development of SCOS. In this review, we present the research findings related to SCOS etiology, including genetics, epigenetics, signaling pathways, and endocrinology of this disorder.

Genetic causes of SCOS

Genetic disorders associated with male infertility include chromosomal abnormality, Y chromosome microdeletions, mutations, polymorphisms, and epigenetic disorders. Known genetic abnormalities contribute to 15–20% of the most severe forms of male infertility [35]. Stouffs et al. (2016) have investigated possible causes of SCOS with a specific focus on genetic alternations. Their results showed in a large part of the patients (>23%), abnormality in the sex chromosomes is involved. Klinefelter syndrome was present in the majority of patients, followed by patients with Yq microdeletions [33]. In addition to these genetic disorders, other genetic modifications have been identified in association with SCOS as follows below (Table 1).

Chromosomal abnormality

Chromosomal alterations are one of the common genetic causes of male infertility. The Klinefelter syndrome (47, XXY) is the most frequent abnormality, that is related to sex

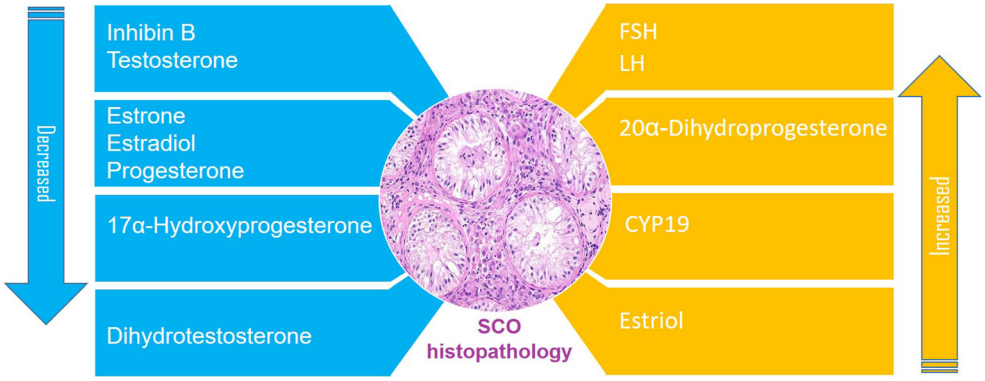

Fig. 1 Schematic representation of the hormones level alternation in SCOS, based on available studies. Abnormalities in the hormonal regulation of spermatogenesis may contribute to the SCOS pathophysiology

Table 1 Genetic abnormalities observed in human Sertoli cell-only syndrome

Genetic abnormality	References
Chromosome abnormalities	
Klinefelter syndrome (47, XXY)	[34]
45, X/46, XY mosaicism	[36]
46, XX male	[37]
Chromosome rearrangements	[38]
Isochromosome Yp	
Paracentric inversion of chromosome 7 (q22-31) and 12 (p12q12)	[39, 40]
Duplication in chromosome 19p13.3	[41]
Y chromosome microdeletions	
AZFa	[42]
AZFb	[43]
AZFc	[44]
Gene mutations	
USP9Y	[45]
USP26	[46]
DBY	[45]
HOXD9	[7]
SYCE1	[7]
COL1A1	[7]
H19	[7]
KCNQ1	[7]
PLK-4	[47]
CX43	[48]
FANCM	[49]
ETV5	[50]
H-MSI	[51]
MMR	[51]
CAG repeat in *AR* gene	[52]
SNPs	
ETV5 (+48845 G>T)	[53]
FGF9 (c.-712 C/T)	[54]
LRWD1 (3 coding SNPs)	[55]
SEPTIN 12 (8 coding SNPs)	[56]
RAD21L (coding SNP)	[57]

chromosomes aberration. The prevalence of Klinefelter syndrome is about 2/1000 male births [58] and usually is associated with SCO histopathology. However, autosomal anomalies like Robertsonian and reciprocal translocations and inversions are also involved in male infertility [59]. 45, X/46, XY mosaicism is one of the rare chromosomal alterations with a wide phenotypic spectrum. There is a subgroup of this mosaicism that has a normal male phenotype and is usually diagnosed during infertility investigation [60]. It has been reported that testicular biopsy of males with this mosaicism showed SCO histopathology [61]. Another chromosomal disorder that is associated with SCOS is 46, XX male, in which an unequal crossing over occurs between the short arms of the X and Y sex chromosomes during the gametogenesis, results in an abnormal X chromosome containing the SRY gene [36]. The SRY positive XX male syndrome is usually diagnosed in adult infertile men during infertility investigations. A rare case of 46, XX male with ambiguous genitalia and SCOS was reported [62]. Chromosomal rearrangement appears to impact spermatogenesis. Very rarely structural rearrangements of the Y-chromosome, the isochromosome of Yp observed in a man with SCOS [37]. It has been reported that duplications in chromosome 19p13.3 had the highest frequency in patients with SCOS [38]. Paracentric inversion of chromosome 7 (q22–31) [41] and chromosome 12 (p12q12) [39] were reported in association with SCO histopathology.

Mutations

It has been demonstrated that a large percentage of SCOS may be related to Yq11 (AZFa sub-region) microdeletions [40, 42, 61, 63–66]. The massive deletions in the AZFb or AZFb+c regions are one of the important genetic causes of SCO [67]. It has been demonstrated that a very high incidence of AZFc deletions exists in incomplete SCOS [43]. The absence of ubiquitin-specific protease 9Y (*USP9Y*) gene that is located in the AZFa region of the Y chromosome is often associated with blockage of spermatogonial cell proliferation causing SCOS in adults. However, the ubiquitin-specific protease 26

(*USP26*) gene is an X-linked gene specifically expressed in testis and its alternation has been reported in SCOS [44]. Patients with deletion of both *USP9Y* and *DBY* (DEAD/H box polypeptide, Y chromosome) had azoospermia with testicular histology of SCO [63].

Investigation of autosomal genes defects in SCOS revealed amplifications and deletions in several genes including *HOXD9*, *SYCE1*, *COL1A1*, *H19*, and *KCNQ1* are associated with SCOS and might be implicated in this disorder [7]. A heterozygous 13-bp deletion in the Ser/Thr kinase domain of Polo-like kinase 4 (*PLK-4*) has been reported in a man with SCOS [46]. This kinase is one of the key regulators of centriole duplication. Connexin 43 (CX43) is a gap junction protein expressed in the blood-testis barrier that affects the maturation of Sertoli cells and the process of spermatogenesis [45, 68]. The absence of CX43 expression in human Sertoli cells is associated with SCOS and impaired spermatogenesis [47], but the responsible mechanism is unclear. Using in vitro hiSC model, Liang et al. revealed that the absence of CX43 disrupts multiple molecular pathways, including lipid metabolism and nucleobase catabolism in Sertoli cells [69].

It has been reported that the human male Bi-allelic Recessive Loss-of-Function Variants in *FANCM* (Fanconi anemia complementation group M) is possibly linked to SCOS [70]. ETS (E twenty-six) variant gene 5 (*ETV5*; alias ETS-related molecule) belongs to a family of transcription factors that regulate promoter activities of genes involved in many cellular functions [71]. It has been demonstrated that *ETV5* gene mutations are associated with SCOS [48]. Maduro et al. (2003) reported for the first time significance of high microsatellite instability (H-MSI) and DNA mismatch repair (MMR) protein defects are present in azoospermia, predominantly in SCOS [49].

Mutations in the androgen receptor (AR) gene cause a variety of defects related to male infertility. The investigation of androgen receptor CAG and GGN repeat lengths in men with spermatogenic impairment showed that the CAG 21 allele seems to increase the risk of idiopathic SCOS [72]. Copy number variants (CNV) were evaluated by array-CGH in patients with SCOS which was the first CNV study in male infertility. They found sex-chromosomal, mostly private CNVs were significantly overrepresented in SCOS and 4 additional candidate genes, and two regions without known genes were related to SCOS [50]. On the other hand, no known infertility-related copy number variations were found by array comparative genomic hybridization technique in a selected group of idiopathic SCOS [33].

It has been found that loss of the Nupr1 protein leads to testicular development of a SCOS-like phenotype in the mouse model [51]. The transcription factor FOXJ3 (Forkhead box J3) is highly expressed in spermatogonia and meiotic spermatocytes in the mice testes. *Foxj3* knockout mice that *Foxj3* was deleted from spermatogonia exhibited complete sterility and SCOS in males [52]. CUL4B belongs to the CRL4 subfamily, and the CRL complex plays a critical role in the survival of germ cells [73]. The *CUL4B*-null mice had SCOS phenotype, but Miyamoto et al. reported no significant mutations in *CUL4B* in these patients with SCOS [74]. So mutation in some genes in animal models could not be applied to humans.

Epigenetic alternations Misregulation of epigenetic modification has been detected in association with SCOS. It has been reported that the presence of highly acetylated histone H4 in testicular sections with SCO pathologic pattern [75]. In an epigenetic disorder, Prader-Willi syndrome, testicular histology in childhood sometimes showed SCOS [76, 77].

Single nucleotide polymorphisms Several single nucleotide polymorphisms (SNP) have been identified in association with the SCOS. The homozygous TT allele of the +48845 G>T variant in the *ETV5* gene confers a higher risk of male infertility associated with SCO and NOA in Australian men [78]. Studies from fibroblast growth factor 9 (*Fgf9*) knockout mice confirmed the crucial roles of FGF9 in male sex determination and gonadal development [79]. An association between aberrant expression of *Fgf9* gene with SCOS was reported. *Fgf9* expression was significantly decreased in patients with SCOS as a result of a promoter polymorphism (c.-712C/T) of the *FGF9* gene, which could be one of the causes of its low expression [80]. The human *LRWD1* (leucine-rich repeats and WD repeat domain containing 1) gene is critical for the initiation of pre-replication complex assembly. The association of defects in this gene with SCOS was investigated. No mutations were detected in *LRWD1*; however, three coding SNPs were found in the SCOS patients [53].

Septin12 (*SEPTIN12*) is a member of the septin family of cytoskeletal GTPases that form filamentous structures in interphase cells and express specifically in the testis. The association of *SEPTIN12* gene defects with SCOS was investigated. They found no mutations; however, 8 coding SNPs were detected in the patients with SCOS [81]. *RAD21L* gene is suggested to be a canonical cohesion subunit that is transcribed in the testis. It has been reported that coding SNPs in this gene was notably higher in the patient with SCOS in comparison to the control group [54]. However, testis-specific cytoplasmic poly(A) polymerase beta (*PAPOLB*) is known as a critical factor for spermatogenesis. A study suggested a lack of association of *PAPOLB* polymorphisms with SCOS in humans [55].

MicroRNAs in SCOS

MicroRNAs (miRNA), a new class of endogenous small RNA molecules, are important posttranscriptional regulators of

gene expression. A little is known about their involvement in human spermatogenesis. In the animal model, it has been demonstrated that miRNAs play critical roles in male germ cell development [56]. It has been reported that patients with SCOS showed a large number of deregulated miRNAs that might be due to the absence of germ cells in these patients. Members of the miR-517a/b/c family which is known to be a regulator of genes that control cell proliferation and survival [57] were deregulated in SCOS patients [82]. It has been reported that 174 miRNAs were distinctly expressed in Sertoli cells of SCOS compared with OA. They suggested that these miRNAs may be novel insights associated with the pathogenesis of SCOS [83]. In another study, miR-202-3p was upregulated in Sertoli cells of SCOS patients compared with OA patients. This microRNA directly targets the Wnt/b-catenin signaling pathway, induced Sertoli cell apoptosis, and inhibited cell proliferation [84].

Signaling pathways

Signaling pathways, a series of chemical reactions that control cell functions, and their disorders might be involved in SCOS pathophysiology. Summary of signaling pathways involved in SCOS pathophysiology is presented in Table 2. Caspases are a family of proteins involved in the apoptotic pathway. When Caspase-3 is activated, there is no return in the apoptotic process and will be disassembled [99]. Increased active caspase-3 was found in SCOS and might be involved in its etiology [100]. It has been demonstrated that the expression of FasL is upregulated in the testis samples of patients with SCOS compared with normal spermatogenesis. Expression of Fas, FasL, and active caspase-3 was detected in Sertoli cells and hyperplastic interstitial cells of SCOS patients. This led to trigger apoptotic depletion of Fas-expressing germ cells in SCOS [101]. Phosphoribosylpyrophosphate synthetases 2 (PRPS2) expression in patients with SCOS was significantly greater than normal spermatogenesis. PRPS2 overexpression significantly inhibited cell apoptosis via p53/Bcl-2/caspases signaling pathway and promoted cell cycle transition. So, PRPS2 might be one of the potential novel proteins associated with SCOS [102]. Expression of SAM68 (Src-associated substrate in mitosis of 68 kD, also known as KH-DRBS1) at mRNA and protein levels was absent or barely detectable in testicular tissues of all patients with SCOS. This protein regulates a range of processes and decreased expression of Sam68 may suppress germ cell proliferation and induced apoptosis [85]. The expression of galectin-l and -3 (vertebrate lectins interacting with B-galactosides) and galectin-specific binding sites were found to be increased in Sertoli cells in SCOS compare to normal human testis might have a connection to the control of apoptosis [86].

Fibroblast growth factor-5 (FGF5) is a growth factor that could promote spermatogonial stem cell (SSC) proliferation via ERK and AKT activation. FGF5 was downregulated in SCOS compared to OA patients [87]. The TGF-β pathway

Table 2 List of signaling pathways involved in SCOS pathophysiology

Proteins	Expression status	Signaling pathway/function	Reference(s)
Caspase 3	↑	Apoptosis	[85]
FasL	↑	Apoptosis	[86]
PRPS2	↑	Inhibition of apoptosis in Sertoli cells	[87]
SAM68	↑	Apoptosis	[88]
Galectin 1, 3	↑	Apoptosis	[89]
FGF5	↓	Cell proliferation	[90]
TGF-β		TGF-β/EGFR signaling	[91]
GDNF, FGF8, BMP4	↓	Proliferation and differentiation of SSCs	[92]
RAB20, RAB3D, RAB40B,RRAS2, HRAS, and catalytic subunit of PI3CA and PI3K	↓	Vesicular traffickingR	[92]
RohB	↓	Cell signaling	[93]
APC/C	↓	Cell cycle	[94]
IGF1/PI3K/AKT	↑	Cell cycle	[94]
S-COMT	↑	Metabolizing of estrogen	[95]
SOX9, AMH	↑	Androgen/AR	[96]
AR	↓	Androgen/AR	[96]
CYP19A1	↑	Androgen/estrogen level regulation	[97]
CYP17A1	↓	Androgen/estrogen level regulation	[31]
SOAT, OATP6A1, OSCP1	↓	Androgen/estrogen level regulation	[98]

and the interaction between TGF-β and EGFR signaling may play a role in the dysfunction of Sertoli cells in SCOS and contribute in the pathogenesis of this disorder [88]. It has been suggested that overexpression of BMP4 might be related to the SCOS. They identified BMP4 as the first autocrine factor controlling the development and function of adult human Sertoli cells [89]. Paduch et al. (2019) provided the first detailed comparison of the transcriptomes of human testes with normal spermatogenesis to the testes with SCOS and identified deficits in gene expression by Sertoli cells. They focused on 244 transcripts as human Sertoli cell signature transcripts and found that 31% were expressed at significantly lower levels. They concluded that Sertoli cells of SCO testes express abnormally low levels of GDNF, FGF8, and BMP4 that regulate replication and differentiation of SSCs. Reduced expression of genes that act in vesicular trafficking regulation pathways and proteins that polarize and organize the Sertoli cell plasma membrane. This data indicated that SCOS is associated with multiple deficits in Sertoli cell gene expression [90].

Ras homologous B protein (RhoB) belongs to the Ras homologous subfamily are regulatory molecules involved in various cell signaling pathways. Decreased expression of RhoB protein was observed in the Sertoli and Leydig cells in the testis of SCOS patients and suggests the involvement of RhoB in the human spermatogenesis [91]. SCOS pathogenesis could be due to defects in the cell cycle or hormone-mediated pathways in Sertoli and Leydig cells. Recently, it has been suggested that SCOS may be caused by disordered APC/C-mediated cell cycle progression and PI3K/AKT signaling. It has been reported that downregulation of APC/C-mediated cell cycle progression in the spermatogonia and upregulation of IGF1/PI3K/AKT signaling in Sertoli cells is a driver of SCOS development [103].

It has been reported that testicular expression of S-COMT, the estrogen-metabolizing enzyme, was elevated in seminiferous tubules of SCOS patients. Increased expression of this enzyme may be related to high intratesticular 2OHE2 and 2ME2 concentrations, which could negatively affect the function of Sertoli cells and spermatogenesis [92]. Upregulation of SOX9 and AMH proteins but downregulation of AR proteins in Sertoli cells due to defect of androgen/AR signaling is detected in patients with SCOS. This finding explains the immaturity of Sertoli cells in SCOS patients with low serum testosterone levels and demonstrates a role for SOX9 and the regulation of SOX9/AMH by AR signaling in the pathogenesis of SCOS [93]. It has been shown that SCOS patients with low T/LH ratios and Leydig cell hyperplasia have Leydig cells that overexpress *CYP19A1*, leading to increased intratesticular E2 levels and E2/T ratios [94]. So impaired androgenic production in SCOS is associated with depressed CYP17A1 expression, possibly regulated by E2. It has been demonstrated that Leydig cells of men with SCOS and testicular steroidogenic dysfunction show discordance between transcriptional and protein expression of CYP17A1, associated with impaired T production and elevated intratesticular E2 levels. Thus, Leydig cell dysfunction is associated with post-transcriptional deregulation of CYP17A1 in patients with SCOS [95]. It has been reported mRNA expression of steroid sulfate carriers to include the Sodium-dependent Organic Anion Transporter (SOAT), the Organic Anion Transporting Polypeptide 6A1 (OATP6A1), and the Organic Solute Carrier Partner 1 (OSCP1) in human testis with SCOS were significantly lower or even absent. Significantly lower expression of SOAT may cause a disturbed transport of sulfated steroids and consequently, disrupt the local supply of androgens and estrogens [96].

Other etiologies

Environmental agents such as temperature during testicular development, as in cryptorchidism situation, could cause the disappearance of the germ cell and create SCOS [97]. Some of the other involved factors are the destruction of germ cells by the action of X-ray irradiation [98] or chemical agents such as hormonal treatment [104] and chemotherapy in cancer treatment. Estrogen therapy reduces serum concentrations of testosterone and gonadotropins [105] and causes the transformation of mature Sertoli cells to undifferentiated Sertoli cells. It has been suggested neural elements (neuronlike cells) may be involved in SCOS pathogenesis; however, the underlying mechanisms were unknown [106]. SCO may be the final stage of persistent, longstanding testicular parenchymal hypoxia, which deteriorates sperm production over time [107]. So impairment in venous drainage of the male reproductive system can cause SCOS. Alcohol induces disorders in the human testis, and it has been suggested some cases of heavy alcohol drinkers had SCOS [108].

It has been reported that varicocele in rats can cause SCOS. Laboratory varicocele caused progressive impairment of the testes, and SCOS could be induced when the damage was severe [109]. Hypothermic testicular ischemia also could produce SCOS in animal models [110].

Diagnosis and clinical management

Azoospermia occurs in 10–15% of males seeking medical care for infertility [3]. After confirmation of azoospermia based on the examination of multiple semen specimens, clinically distinguishing NOA from OA can be done by the analysis of diagnostic parameters, including history, physical examination, and hormonal analysis. These parameters provide a >90% prediction of whether azoospermia is obstructive or non-obstructive [111]. The gold-standard diagnostic test for distinguishing between NOA subtypes (HS, MA, SCOS, tubular sclerosis, and mixed patterns) is a testicular biopsy and

subsequent histopathologic examination of biopsy specimens. Each of these subtypes has a different prognosis for infertility treatment. The diagnosis and management of SCOS, which is the subject of this review, are described in more detail below.

Clinical parameters and genetic testing

The clinical characteristics of SCOS patients vary widely regarding history, physical examination, and hormonal profile. On physical examination, except for Klinefelter syndrome, other patients have normal secondary male sexual characteristics, and no gynecomastia is seen. For all patients with azoospermia, serum level of FSH, LH, and total T is obtained. The testes volume can be normal or smaller in size, and some patients have higher levels of FSH than normal [33]. In a study, it has been shown that when testicular biopsies showed bilateral SCO, the patient had azoospermia (86%) or oligozoospermia (14%). The testicular size was normal in 36%, and the FSH level was normal (43%), raised (21%), or grossly elevated (more than twice normal, 36%) [112]. So the clinical features associated with the SCO histology are extremely variable. On the other hand, when one biopsy shows SCO, the opposite testis appearance could vary from impaired spermatogenesis to almost normal spermatogenesis [112].

Genetic tests include cytogenetic karyotyping and molecular diagnosis and subtyping of Y chromosome microdeletions are usually recommended to all men with NOA. The karyotype of most SCOS men is normal, while SCOS may be a result of Klinefelter syndrome, microdeletions in the Y chromosome, and other genetic causes. Deletions that remove the entire AZFa are associated with the pure SCO with no residual areas of complete spermatogenesis. Although partial AZFa deletions may be associated with residual spermatogenesis in the testis [113]. However, for many of these patients, the possible genetic cause is unknown. Some genetic causes reported in associations with SCOS are described in the etiology section of this review but are not yet applicable in clinical practice.

Testicular biopsy

The exact diagnosis of SCOS is based on diagnostic testicular biopsy and histopathological examination. Histologic examination is performed on paraffin-embedded and hematoxylin and eosin-stained samples by examining at least 100 different sections of seminiferous tubules. When no germ cells are present in the seminiferous tubules except Sertoli cells, but the tubular architecture is not affected by fibrosis; SCOS is diagnosed [114]. Two distinct histologic patterns of SCO, namely primary and secondary, also can be identified by histologic examination. These two patterns of SCO have a different prognosis for sperm retrieval, and their differences are described in more detail in the histopathology section.

Clinical management

SCOS patients do not have therapy options to cure their disorder and help them to have a biological child. However, Paulis et al. (2017) reported an infertile couple case in whom the male has SCOS that with FSH hormone treatment, several sperms were observed in testicular biopsy achieved by testicular sperm extraction (TESE). After ICSI and subsequent embryo transfer, the live birth of a girl resulted [114]. Nonetheless, based on current knowledge, there is not enough evidence and this does not apply to all SCOS cases. Another intervention before sperm retrieval in NOA patients is varicocele repair. In NOA men with varicocele, varicocelectomy may offer an opportunity to have motile sperm via ejaculate. Significant improvement in testicular histology has been reported after varicocele repair in NOA patients [115]. There have been some studies regarding motile sperm obtained in SCOSpatients after varicocele repair [116, 117]. On the other hand, some studies showed no improvement in SCOS after varicocelectomy [118–120]. Therefore, varicocele repair in patients with SCOS, unlike other NOA subtypes such as HS and MA, has been very little if any effect on sperm recovery.

SCOS affects about 26.3–57.8% of azoospermic patients [5, 6], and sperm could be found in the seminiferous tubules of 20% of these men using testicular sperm extraction procedure [121]. Many SCOS patients have rare foci of complete spermatogenesis in the testes so, surgically testicular sperm retrieval combined with ICSI is an option for infertility treatment in these patients. Two different histological patterns of SCOS are the primary and the secondary forms with different prognoses to testicular sperm extraction. The definitive diagnosis of these patterns is by diagnostic testicular biopsy. Successful sperm retrieval rate in incomplete and complete germ cell aplasia has been reported 86.0% and 19.3%, respectively [122], which can be successfully used for ICSI. So, secondary forms of SCOS have a better prognosis in testicular sperm retrieval.

In addition to fertility issues, it has been reported that the prevalence of testicular nodules and cancer in men with complete SCOS is very high [123]. So, because of the increased risk of cancer in the testes with complete SCOS, a biopsy for the histological examination should always be performed. The future preconception genetic testing of parents, as mutation carriers, or preimplantation genetic testing of embryos may be needed for identifying possible carriers. This provides more information for couples about whether or not the syndrome could be passed on to their children. Also, there is not enough data on the health of SCOS patients' offspring, and long-term follow-up studies are needed in this regard.

Sperm retrieval and prognostic factors

Patients with SCOS are infertile due to non-obstructive azoospermia. Before describing the microdissection testicular sperm extraction (micro-TESE) technique by Schlegel in 1999 [124], the preferred sperm retrieval method in NOA patients was conventional TESE. The removal of large fragments of testicular tissue in TESE may compromise androgen production [125] and had tough laboratory processing [126]. In the micro-TESE procedure, the surgeon is looking for a dilated and opaque seminiferous tubule that might be containing sperm. This method has fewer complications than TESE and more sperm retrieval rate, especially in SCOS patients. It has been demonstrated that the sperm retrieval rate in SCOS by TESE is lower than in patients with NOA in general, and micro-TESE increases the sperm retrieval rates. In a systematic review, it has been shown more favorable sperm retrieval in SCOS for micro-TESE when compared with conventional TESE [127]. Retrieved sperm in SCOS patients can be immediately used for ICSI or cryopreserved for future ICSI attempts. ICSI achieved similar live birth rates in patients with SCOS, like other patients with NOA [128].

After testicular sperm extraction, for most SCOS patients with failed sperm recovery, assisted reproductive techniques such as ICSI will be impossible. For men with complete AZFa, AZFb, or AZFbc, the chance of sperm retrieval success is virtually nonexistent, and usually proceeding with sperm retrieval is not recommended. Hormonal concentration, testicular volume, and histologic diagnosis are not informative enough to predict the presence of testicular sperm. Serum FSH level is not also a predictor of a successful sperm retrieval, but it can affect the outcome of sperm recovery. It was shown that those men with higher FSH had a more successful sperm retrieval by micro-TESE [129]. Telomerase enzyme activity has been detected in male germ cells. In testicular samples with haploid cells, higher telomerase activity was detected [130] while patients with SCOS showed no telomerase activity. In a retrospective cohort study that included 640 patients with pure SCOS who underwent micro-TESE, 44.5% of patients had successful sperm retrieval. No difference was observed in sperm retrieval rates based on testis volume, but patients with ≥ 15cc testicular volume and FSH 10-15 mU/mL had the worst prognosis, with a sperm retrieval rate of 6.7% [131]. Intraoperative measuring the diameter of seminiferous tubules during micro-TESE is a useful predictor for sperm retrieval in NOA patients. However, in SCOS patients, it has been reported that the sperm retrieval rate in men with a tubule diameter ≥100 μm was lower than that in those with <100 μm. The sperm retrieval rate from the contralateral testis in men with a tubule diameter ≥100 μm, also was lower than that in those with <100 μm [132]. This finding appears to conflict with previous reports that showed sperm recovery is higher in dilated tubules.

It still is a challenge to identify patients who have a better chance of successful testicular sperm extraction. Parameters include age, infertility time, serum FSH, LH, testosterone levels, and testicular volume were not useful to predict sperm retrieval. Therefore, it is necessary to use a suitable biomarker for predicting testicular sperm presence in testes and identifies those patients with real chances of a positive sperm recovery result on the future biopsy. This prevents unnecessary testis operation and its side effects. Specific markers in seminal plasma may reflect the cumulative yield of spermatogenesis in testes and thus be useful to detect focal spermatogenesis. Many studies have been done and are being done and gain insight into the origin of SCOS may be helping in this regard. In cases with no mature sperm retrieved, in vitro culture of preexisting immature germ cells has been proposed. On the other hand, some of the pure types of SCOS patients have no germ cells, the only possible way to have biological offspring would be the use of their somatic cells via induced pluripotency to generate germline and in vitro spermatogenesis [133]. Further studies are needed to develop this method, and there is a long way to go before it can be used clinically.

Future perspectives

Further studies are needed to understand the molecular pathways of genes involved in the SCOS. Recently, the iPSC cell line HUSTi002-A generated from fibroblasts of a SCOS patient who carries a homozygous *PIWIL2* mutation offers an opportunity to study the roles of the *PIWIL2* gene in the pathogenesis of SCOS [134]. In a functional proteomics study, it has been identified 13 differential proteins in testis samples of SCOS compared to normal spermatogenesis. Among these differential proteins, Heterogeneous nuclear ribonucleoprotein L (HnRNPL) was suggested as a key regulator of apoptosis, death, and growth of spermatogenic cells, by String and Pubgene bioinformatic programs. Further in vitro and in vivo studies revealed that knockdown of HnRNPL led to inhibited proliferation, increased apoptosis of spermatogenic cells but decreased apoptosis of Sertoli cells. So HnRNPL was suggested as a key regulator of spermatogenesis in SCOS [135]. Other proteomics studies revealed that cell cycle and proteolysis, and RNA splicing were the most significant biological processes impaired by suppression of related proteins in SCOS. This study provides novel candidate proteins associated with SCOS, including 298 and 76 down- and upregulated protein changes, respectively. From these altered proteins, 57 were highly downregulated and 3 were highly upregulated. It has been demonstrated that spliceosome, cell cycle, and proteasome proteins, as well as energy and metabolic involved proteins, are highly suppressed in SCOS patients [136].

Cell-free seminal mRNA (cfs-mRNA) contains testis-specific transcripts from bilateral testes and is a novel non-

invasive approach for the classification of azoospermia. It has been reported the presence of DEAD-box polypeptide 4 (DDX4) in cfs-mRNA to identify and characterize the incidence of SCOS is more accurate than testicular histopathology [137].

To be the father of a biological child, in vitro maturation of SSCs isolated from SCOS without sperm in their testicular biopsies is a new approach for possible future infertility treatment. In vitro maturation of SSCs extracted from the testis of SCOS patients is one of the new suggested approaches to treat their infertility problem. For the first time, Abofoul-Azab et al. (2019) showed the presence of meiotic and/or postmeiotic cells in biopsies without the sperm of SCOS patients and examined the possibility of inducing spermatogenesis from isolated spermatogonial cells of these biopsies in vitro using 3D MCS. They indicated that isolated cells from some of these biopsies could be induced to meiotic and/or postmeiotic stages under in vitro culture conditions [138]. New researches with the aid of novel technologies will help to more accurately identify the etiology of SCOS and its clinical management in the future.

Conclusion

The available data are insufficient to conclude an accurate and non-invasive way for diagnosis and a definite method for the treatment of all SCOS cases. The clinical features of SCOS are extremely variable. Most of the SCOS patients have a normal karyotype, and some have smaller testes and normal or higher levels of FSH. So it is difficult and sometimes impossible to diagnose SCOS based on clinical characteristics. The exact diagnosis of this disorder is still based on a diagnostic bilateral testicular biopsy. This is an invasive method with complications such as pain and fibrosis. On the other hand, patients with SCOS are infertile due to non-obstructive azoospermia. For the treatment of these patients, testicular sperm extraction is the only option for these men to have their biological child. Frequent failure of sperm retrieval is not acceptable for the infertile couple. It still is a challenge to identify patients who have a better chance of successful testicular sperm extraction. So, there is a need to find a suitable biomarker to diagnose the SCO histopathology without using biopsy and predict testicular sperm presence in the testes. This prevents unnecessary testis operation and its side effects and identifies those patients with real chances of a positive sperm recovery result on the future biopsy. As a non-invasive marker, for example, molecular markers in seminal plasma may reflect the spermatogenesis status in the testes and can be useful to detect rare foci of spermatogenesis. This method does not need a testicular biopsy and will be patients friendly.

This review aimed to provide an overview of the current knowledge regarding SCOS etiology and emphasize the need for future investigation for the management of this disorder. At present, there is no treatment for SCOS patients. SCOS patients with failed surgically sperm retrieval result does not have therapy options to help them having a biological child. In vitro maturation of SSCs isolated from SCOS men without sperm in their testicular biopsies and the use of somatic cells via induced pluripotency to generate germline, are new approaches for possible future infertility treatment in these patients. The reasons for many cases of SCOS are unclear. Recent studies have expanded our understanding of the etiology of the SCOS. There is a need for more research to identify the causes of idiopathic SCOS cases. Finally, more understanding of the etiology of SCOS can help to develop a suitable therapeutic method for the management of this disorder.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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