Current perspectives in hypospadias research: A scoping review of articles published in 2021 (Review)

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Received December 14, 2022; Accepted March 9, 2023

DOI: 10.3892/etm.2023.11910

Abstract. Hundreds of papers are written about hypospadias every year referring to all aspects of the pathology, being one of the most common congenital malformations. The present study conducted a scoping review of articles published in 2021 to present the main issues and summarize current perspectives and achievements in the field. It searched for the keyword 'hypospadias' in the three most popular databases (PubMed, Scopus and Web of Science). After the analysis of the publications, they were categorized into different domains. The present review was performed respecting the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA ScR) guidelines. A total of 284 articles were included. These were published in 142 different journals. The most accessed was the *Journal of Paediatric Urology* with 54 articles. The main identified domains were related to surgical techniques, postoperative care, complications, anesthesia, anatomical factors, genetics, environmental factors, endocrinology, associated malformations, questionnaires and recommendations, management, biological materials, animal models, retrospective studies of centers, social media, bibliometrics, small gestational age, neoplasm, or fertility. Promising modifications of existing surgical techniques were presented with improved outcomes for both the proximal and distal types of hypospadias. Relevant anatomical and etiological, and also genetic factors were clarified. Aspects of the peri- and postoperative management referring to the antibiotherapy, analgesia, dressing techniques, and the future use of novel bioengineering agents to prevent, reduce or treat the occurring complications were discussed.

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Key words: hypospadias, hypospadias repair, 2021, pediatric surgery, updates

Contents

1. Introduction

Hypospadias is a congenital malformation, in which the meatus is opening on the ventral aspect of the penis, at different possible levels. Usually, the malformation is more complex and may be associated with penile curvature, glans deformation, narrow meatus or megameatus, and anomalies of the skin. Severe cases can present other urogenital or chromosomal anomalies. There are a number of unknown aspects of this malformation's etiology and development (1,2). Hypospadias repair may be a routine operation in distal cases and can be very challenging in proximal cases, even for a trained surgeon. There is no consensus on the treatment options for hypospadias and the development of treatment guidelines remains an unsolved file in medicine.

Furthermore, how the penis look is an important somatic and psychological facet of every boy or every family. In these conditions, it is obvious it became a subject of interest in

medicine and a number of doctors from different specialties (especially pediatric surgeons or urologists) have tried to solve the problem (3-5).

In the last 10 years, according to the PubMed platform, an average of 313 (±38) studies were published each year (based on a search for the keyword 'hypospadias'), the number of papers increasing each year. This pathology represents one of the most debated problems and not only among pediatric surgeons (6). For every pediatric surgeon, urologist, and specialist in this field, it is essential to know what is new about hypospadias and be up to date. The present study aims to present this pathology's current perspectives and the most important achievements in hypospadias research during 2021.

2. Materials and methods

The present study protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2022 and was last updated on 23 November 2022 (registration number INPLASY2022110117). It was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA ScR) guidelines.

The present study chose the three most popular platforms (PubMed, Scopus and Web of Science) and searched for the keyword 'hypospadias'. All the publications were restricted to 2021. All the results were downloaded in CVS format (or directly as xls format in the case of the Web of Science platform) and processed using Microsoft Excel software. The articles from PubMed were used as a base of the research, PubMed being considered the most accessible and most frequently used database. The duplicate records were removed compared to the results from the other two platforms. The remaining articles were analyzed individually and manually by the three reviewers.

The present study included all the articles which were published in 2021 in the research field of hypospadias with valuable information relating to surgical techniques, postoperative care, complications, anesthesia, anatomical factors, genetics, environmental factors, endocrinology, associated malformations, questionnaires and recommendations, management, biological materials, animal models, retrospective studies of centers, social media, bibliometrics, small gestational age, neoplasm, or fertility. Articles which were written in English were accepted. Papers in other languages were accepted if they had an English abstract with valorous information. Papers which were published in a year other than 2021, were outside of the research field, or were referring to other pathologies were excluded. However, those articles which were published in print format in 2022 and online in 2021 were considered as 2021 articles. Books, commentaries, responses to other papers, errata and withdrawn articles were excluded.

Source selection (both at title/abstract screening and full-text screening) was performed by the three reviewers independently (HG, ZB and ED). Any disagreements were solved by consensus or by the decision of the fourth reviewer (ZD). The process was accompanied by a flowchart detailing the flow from the search, through source selection, duplicates, retrievals, and any additions. The workflow is shown in Fig. 1.

The present study extracted from every qualified paper the essential ideas and conclusions. Then, this information was arranged and grouped into categories, some of them even into subcategories. The main information of the papers on the same topic with similar conclusions was merged, reformulated, and included in the corresponding table. The databases were accessed for the last time on the 20 November 2022. The number of references and the number of included articles differ as in the introduction some papers were cited to describe hypospadias in general.

The conclusions from the included articles relating to hypospadias research were categorized into 18 chapters: Surgical techniques (Subgroups: proximal hypospadias repair, distal hypospadias repair, covering tissue, curvature, fistula and stenosis, reoperative techniques, others), Postoperative care, Complications, Anesthesia, Anatomical factors, Genetics (reviews, genetical research on a population or on hospitalized patients, genetic counseling, genetic syndromes and malformations, genetical and histological analyses), Environmental factors, Endocrinology, Associated malformations, Questionnaires and recommendations, Management, Biological materials, Animal models, Retrospective studies of centers, Social media, Bibliometrics, Small gestational age, Neoplasm, and fertility.

3. Results

A total of 284 articles were included. These were published in 142 different journals in 2021. The most accessed journal on this topic was the *Journal of Paediatric Urology* with 54 articles (37.75% of the analyzed publications), followed by the *World Journal of Urology* (nine articles), the *African Journal of Urology* (eight articles), *Journal of Paediatric Surgery* (eight articles), *Urology* (seven articles), *Research and Reports in Urology* (seven articles), *Journal of Urology* (seven articles), *Frontiers in Pediatrics* (seven articles), *Andrologia* (six articles), *Cureus* (five articles). All the other publications had fewer than five papers.

The studies were classified in the described manner and 71 referring to surgical techniques (Subgroups: 27, proximal hypospadias repair; 18, distal hypospadias repair; seven, covering tissue; four, curvature; nine, fistula and stenosis; three, reoperative techniques; and three, others), 18 to postoperative care, 16 to complications, 13 to anesthesia, 22 to anatomical factors, 41 to genetics (three, reviews; 21, genetical factors; six, genetical research on a population or on hospitalized patients; four, genetic counseling; five, genetic syndromes and malformations; and two, genetical and histological analyses), 19 to environmental factors, 11 to endocrinology, nine to associated malformations, 20 to questionnaires and recommendations, six to management, six to biological materials, 11 to animal models, 11 to retrospective studies of centers, three to social media, three to bibliometrics, two to small gestational age and two to neoplasm and fertility.

4. Surgical techniques in hypospadias repair

Surgical techniques represents the most important chapter. A number of them refer to proximal hypospadias repair, which is considered the most challenging among surgeons. There were no new techniques described, but modifications

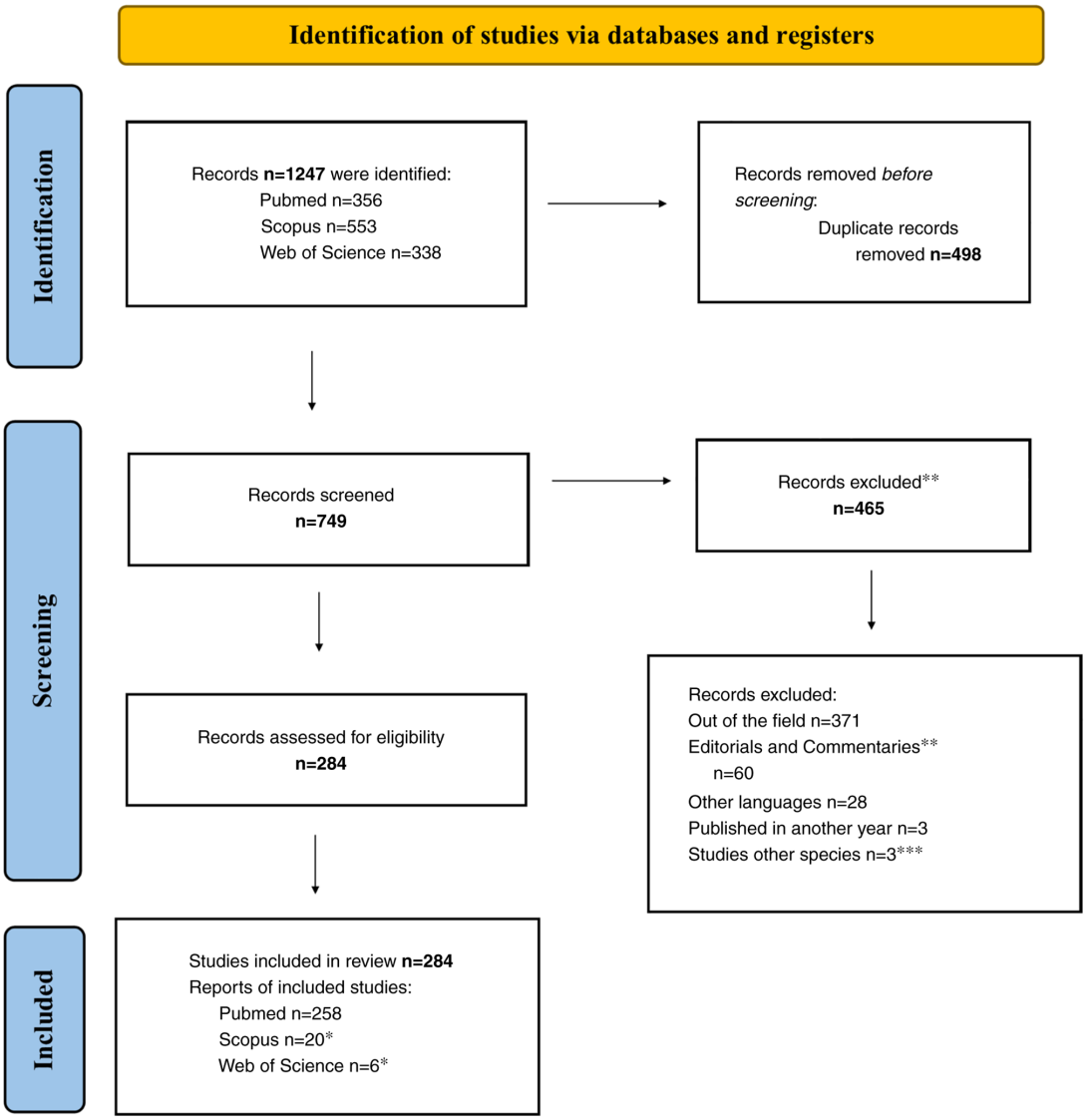

Figure 1. Diagram of workflow. *Without duplicated articles; **books, errata and withdrawn articles; ***Non-human research.

were mentioned by different authors in hope of an improved outcome and reducing the complication rate (7-9). The majority of studies concluded that two-stage surgery leads to improved results compared with one stage (9-12). The options described are modified Koyanagi technique (13-15), transverse preputial island flap urethroplasty (10,12,16), inlay (17-19), or buccal mucosa graft (20,21). Tunica vaginalis represents a good coverage material (22-24). Scrotal raphe may be considered as a reserved option in cases of lack of skin (25). The urethroplasty in proximal hypospadias has improved results when stops at the balanic sulcus. There is only one study that proposes a three-stage urethroplasty (26).

Referring to distal hypospadias, tubularized incised urethroplasty remains the most common and indicated operation (27-31). Dorsal inlay graft urethroplasty (17,19), onlay preputial flap (19) and hybrid Mathieu urethroplasty are mentioned techniques (32,33). A number of authors in the last years prefer the simple advancement of the meatus instead of a proper urethroplasty.

Neourethral covering tissues are effective to prevent complications: tunica vaginalis, dartos, or Buck's fascia are well-known, they can be used in one or two layers. Dorsal plication remains the most used and simple approach to ventral curvature (34).

Table I presents the summaries of the articles about surgical techniques in hypospadias repair.

5. Postoperative care

Post-operatory care was also a debated issue. In some authors' opinion, stented or un-stented repair may lead to a similar outcome, especially in the case of distal hypospadias (28,85). The type of the dressings was not considered as important, although a number of substances were enumerated by different authors to increase their efficacy. Using compound Chamomile and Lidocaine hydrochloride gel, Aloe vera, or autologous platelet gel might decrease pain and edema, reduce inflammation and fibrosis, tubular finger oxygen-enriched oil inside-coated device decrease complications (86,87). Hyperbaric oxygen therapy may help in wound healing (88,89). The number of diapers used is not important for the surgical outcome, but a good washing of genitalia before and after

Table I. Summary of the articles about surgical techniques in hypospadias repair.

Proximal hypospadias		
Author, year	Conclusions	(Refs.)
Wang *et al*, 2021	Proximal hypospadias operated with transverse preputial island flap urethroplasty: those who benefit from incised urethral diversion had improved outcomes compared with those with transurethral diversion.	(8)
Ali MM *et al*, 2021 Zhu X *et al*, 2021 Lin *et al*, 2021 Zhu XJ *et al*, 2021 Ali and Anwar, 2022	Staged (two-stage) transverse preputial island flap urethroplasty has improved results compared with one-stage surgery.	(10) (12) (16) (35) (36)
Chan *et al*, 2021	Proximal hypospadias repairs in two stages: Pedicled preputial flaps and inlay grafts are superior choices compared with Byars' flaps.	(11)
Zhu *et al*, 2021	Transected urethral plate and transverse preputial island flap are good techniques in severe hypospadias.	(12)
Madec *et al*, 2022 Aziz Tamer *et al*, 2021	A two stage procedure Koyanagi urethroplasty allows good final results.	(13) (37)
Vu *et al*, 2021	Results of the one-stage proximal hypospadias repair with modified Koyanagi technique in a single Vietnam center.	(14)
Acimi *et al*, 2021	Despite the modifications added by Snow and Hayashi to Koyanagi urethroplasty in so-called Koyanagi-Snow-Hayashi urethroplasty, the rate of complications. remains high	(15)
Silay *et al*, 2021	Inlay graft is a good choice, but it is not superior to classic repair.	(17)
Chen *et al*, 2021 Shandilya *et al*, 2021	Urethroplasty with buccal mucosa graft, in the first stage, facilitates the second-stage neourethral coverage and is a good technique.	(20) (21)
Radhakrishnan *et al*, 2021 Akkary *et al*, 2021	The tunica-vaginalis flap is an excellent buttress in severe hypospadias repair.	(24) (39)
Obaidullah *et al*, 2021 Chen *et al*, 2021	Islanded scrotal raphe flap is an option in complicated hypospadias repair with skin. shortage	(25) (41)
Lu *et al*, 2021 Akkary *et al*, 2021	The positioning of the external urethral orifice in the coronary sulcus, and urethroplasty in case of severe hypospadias leads to superior results.	(38) (39)
Ding *et al*, 2021	Prefabricated urethra and pre-implanted urethral plate methods are suitable for the correction of severe hypospadias as staging surgery in children.	(40)
Lyu *et al*, 2021	Spongiosum-combined glanuloplasty reduces the rate of complications in proximal. hypospadias	(42)
Karakuș *et al*, 2021	Vertical plication in penile curvature displaces the urethral plate transection in proximal hypospadias.	(43)
Ndiaye *et al*, 2021	Tubed pedicled preputial island flap (DUCKETT procedure) is associated with a high complication rate.	(44)
Rawashdeh *et al*, 2021	Foreskin transplantation in a two-stage reconstruction between monozygotic twins.	(45)
Blanc *et al*, 2021	Double-face preputial island flap revisited is a reliable one-stage procedure for proximal hypospadias.	(46)
Fahiem-Ul-Hassan *et al*, 2021	Single-stage urethroplasty is a versatile approach for different types of hypospadias, with a fistula rate of 12.8%. Posterior hypospadias, pyuria, and longer urethral defect are associated with higher rates of fistula formation.	(47)
Keshk *et al*, 2021	The modified Koyanagi one-stage repair of proximal hypospadias uses a dartos muscle flap as a cover for the urethroplasty improves the results and minimizes. complications	(48)
Tudu *et al*, 2021	The outcome of pediatric urethroplasty was favourable with routine use of intermediate vascularised flap in proximal hypospadias repair.	(49)
Long *et al*, 2021	Masculinizing genitoplasty in children with genital atypia, even if the parents opted for early surgery, is associated with 41% complications in cases of severe hypospadias, in a multicentric study.	(50)

Table I. Continued.

Distal hypospadias		
Author, year	Conclusions	(Refs.)
Omran *et al*, 2021	Dorsal inlay graft urethroplasty (DIGU) has improved surgical outcome compared with Onlay preputial flap (LOF).	(19)
Taneli *et al*, 2021	Tubularized reconstructed plate urethroplasty (TRPU) is an alternative for distal hypospadias repair, without incision or grafting.	(27)
Khirallah *et al*, 2021	Hybrid Mathieu urethroplasty: the Mathieu technique associated with incision of the urethral plate.	(32)
Fahiem Ul-Hassan *et al*, 2021	Buck's fascia repair with wingless glanuloplasty is a good technique with low fistula rates and glanular dehiscence	(47)
Askarpour *et al*, 2021	Meatal advancement glandular with release chordi is superior to Snodgrass methods, regarding the repair of distal hypospadias.	(51)
Edan, 2021	The urethral mobilization technique is a good choice, especially in the case of circumcised patients, the cosmesis and functional results are good and the. complications are less	(52)
Noureldin *et al*, 2021	Predictors of successful outcome of TIP repair are: absence of the chordee, meatus at coronal/subcoronal level, plate width ≥9 mm, AGD >5 cm, patient younger than ≤2 years old, GMS score ≤7, SPL >3.5 cm and grooved glanular shape.	(53)
Abdelhalim *et al*, 2021		(54)
Shoukry *et al*, 2021	Patients with a GMS score >6 have a higher risk of complications. Glans width of ≥14 mm and a penoscrotal length of ≥5 cm is associated with less risk of complication.	(55)
Macedo et a, 2021	The GUD (glandular urethral disassembly) technique (without urethroplasty): disconnects the spongious and the distal urethra from the corpora and detaching partially the glans. The glans is opened in midline. It is followed by cranial mobilization of the urethra with caudal and medial rotation of glans wings.	(56)
Özbey *et al*, 2021	Modeling of the foreskin with the GFC (Glanular-Frenular-Collar) technique to obtain an anatomic aspect.	(57)
Permana *et al*, 2021	TIP urethroplasty leads to good cosmetic and functional outcomes for the cases with megameatus intact prepuce.	(58)
Ahmed *et al*, 2021	The grafted-TIP urethroplasty has comparable results with the classic-TIP in terms of cosmoses, success rate, and complications; grafted-TIP is associated with significantly longer operative time.	(59)
Kızılöz *et al*, 2021	MAGPI under local anesthesia without a catheter is an alternative to the TIP procedure in distal hypospadias repair.	(60)
Alshammari *et al*, 2021	Deepithelialized glans reconfiguration (DeGRe) is a good option for distal hypospadias.	(61)
Zhang *et al*, 2021	Reconstructing forked corpus spongiosum provides excellent outcomes.	(62)
Mohajerzadeh *et al*, 2021	With the exception of the long-term outcomes in cosmetic and functional evaluation, Mathieu incised plate technique is superior to TIP technique.	(63)
Benson *et al*, 2021	A review of long-term outcomes of one-stage augmentation anterior urethroplasty shows worse results than expected.	(64)
Covering tissue		
Tiwari *et al*, 2021	Tunica vaginalis flap or graft is a viable method to repair urethra lesions.	(22)
Favorito *et al*, 2021		(23)
Tessier *et al*, 2021	The more severe the hypospadias, the more effective is the cover the new urethra with flap.	(65)
Rudin *et al*, 2021	The augmentation of the urethral plate of the glans and the distal urethra with the implantation of a wide rectangular free flap in to the meatus, represents an advantage over the implantation of diamond-shaped grafts using the GTIP or TIP graft technique.	(66)
Verma *et al*, 2021	Dartos Flap as an additional cover to TIP is associated with an acceptable complication and has good cosmesis compared with spongioplasty.	(67)

Table I. Continued.

Author, year	Conclusions	(Refs.)
Covering tissue		
Naumeri *et al*, 2021	The covering of neo-urethra by a double dartos layer (compared with a single layer), significantly reduces complications after tubularized incised plate urethroplasty.	(68)
Zhang *et al*, 2021	Buck's fascia with the glans can be used as an integral covering technique in one-stage distal to proximal hypospadias and primary or re-operative hypospadias repair.	(69)
Curvature		
Akdemir *et al*, 2021	Dorsal plication is a relatively simple method with low risk and a high success rate for the treatment of congenital ventral penile curvatures.	(34)
Cetin *et al*, 2021	There are no differences in outcomes between pre-pubertal and post-pubertal boys after correction of penile curvature using corporal plication.	(70)
Kozyrev *et al*, 2021	STAGE technique in ventral curvature penile allows to correct ventral curvature of 15-60˚ with minimal complications.	(71)
Zhou *et al*, 2022	Interposition urethroplasty for glandular hypospadias is a reliable technique. The staged technique had superior outcomes compared with the single-stage technique.	(72)
Fistula and stenosis		
Swatesutipun *et al*, 2021	For urethral stenosis: dorsal transurethral incision, (±dilatation), then oral mucosa	(18)
Furr *et al*, 2021	graft on the defect (±glans preservation) is a feasible technique. Long strictures and	(73)
Favre *et al*, 2021	thickness skin grafts are associated with lower success	(74)
Mershon *et al*, 2021	Recurrent Anterior Urethral Stricture. Augmentation with genital skin flaps and/or grafts or with buccal mucosa is occasionally required. Urinary diversion and perineal urethrostomy has to be considered.	(75)
Sing *et al*, 2022	PATIO technique for small fistulae is more successful compared with standard repair.	(76)
Bar-Yosef *et al*, 2022	Concomitant repair of meatal stenosis and urethral fistula does not increase the risk of fistula recurrence.	(77)
Chatterjee *et al*, 2021	Epithelium of track of the fistula is ablated with a hypodermic needle.	(78)
Shirazi *et al*, 2021	Clamping time for >2 min may prevent bleeding during and after meatotomy.	(79)
Shaw *et al*, 2021	Asopa technique represents an option for augmenting urethral caliber for urethral strictures.	(80)
Reoperative techniques		
Jordan *et al*, 2022	A 3-Stage Approach for the Reoperative Hypospadias. i) Excision and buccal mucosal graft harvest. ii) Dorsal tissue expander placement. iii) The creation of neourethra and skin closure.	(26)
Xie *et al*, 2022	The Mathieu combined tunnel technique for repairing glans dehiscence after failed hypospadias repair is a feasible and reliable procedure.	(33)
Yadav *et al*, 2021	The best treatment for hypospadic meatal stenosis might be a dorsal midline incision, as it does not lead to a proximal shift of the meatus, and heals by reepithelisation without significant scarring, which decreases fistula formation.	(81)
Others		
Samir *et al*, 2021	Running sutures groups was associated with a higher complication rate compared to interrupted sutures.	(82)
Spinoit *et al*, 2021	Redistribution of the abundant dorsal skin and its hooded prepuce to the ventral side of the penis is an option in a number of situations.	(83)
Alaraby *et al*, 2021	Running sutures is a superior suture compare to Vicryl.	(84)

Table II. Summary of the articles about postoperative care.

Author, year	Conclusions	(Refs.)
Abdel-Hamid El-Hawy *et al*, 2021 Scarpa *et al*, 2021	The outcome after stented and un-stented distal urethroplasty reveals similar results.	(28) (85)
Zhang *et al*, 2021	Compound chamomile and Lidocaine hydrochloride gel relieve pain and reduce edema following hypospadias surgery.	(86)
Doluoglu *et al*, 2022	Aloe vera applied to the wound decreases inflammation and fibrosis after the tubularized incised plate urethroplasty model on rats.	(87)
Anand *et al*, 2022	Hyperbaric oxygen therapy prevents wound infection and helps in wound healing and decreases graft failure.	(89)
Donelly *et al*, 2021 Basin *et al*, 2021	Factors associated with opioid prescriptions in postoperative pediatric urology prescription were increasing age and scrotal surgery.	(91) (93)
Cornwell *et al*, 2022	Children undergoing hypospadias surgery usually do not require opioid analgesics and are more likely to endorse pain.	(92)
Ji F *et al*, 2021	Postoperative C-Reactive Protein value (24 h after surgery) is a reliable marker for a possible complication after hypospadias surgery.	(94)
Karakaya *et al*, 2021	Functional and cosmetic results after TIPU are independent of dressing.	(95)
Esposito *et al*, 2021	Dressing using a tubular finger oxygen-enriched oil inside-coated device is effective, easy to manage, cheaper and decreases the rate of complications.	(96,97)
Anand, 2021	Tissue glue-based dressings following hypospadias repair do not represent a major change in postoperative care.	(98)
Elsayem *et al*, 2022	Autologous platelet gel improves outcomes in tubularized incised plate repair and limits surgical complications.	(99)
Murakami *et al*, 2021	Washing the genitals and groin 2 h preoperatively as well as immediately after the removal of a stent, to prevent infections after hypospadias repair.	(100)
Canon *et al*, 2021	The use of perioperative prophylactic antibiotics in hypospadias surgery does not reduce the possibility of infections.	(101)

surgery may be effective (90). The use of opioids or perioperative antibiotics is not relevant for surgical success (91-93). Postoperative C-Reactive Protein value (24 h after surgery) is a reliable marker for a possible complication after hypospadias surgery (94).

Table II presents the summaries of the articles about postoperative care.

6. Complications after hypospadias repair

The most common complications after hypospadias repair remain fistula or stenosis. In some cases, they are easy to treat, but some of them require special interventions with grafts or dilatations and perineal diversion of the urine (28,102,103). For urethra suturing, interrupted sutures are an improvement on running sutures and PDS an improvement on Vicryl (82,104).

Wound dehiscence also remains a debated problem. Factors affecting glanular dehiscence are anatomical (glans width <14 mm, urethral plate width <7 mm), age (before 6 months of age and after puberty), and anesthesia (caudal block). All of these required reinterventions (42,105). Reoperation rate after distal hypospadias repair ranges from 3.3-6.7% (106,107). Other related complications are penile curvature that appears in 25% of cases (>30˚) (43,102,108-110), hairy urethra (111,112), erectile dysfunctions (113,114) and lower urinary tract symptoms (115). There were similar complications every surgeon is acquainted with.

Table III summarizes the articles on complications.

7. Anesthesia

General anesthesia remains the most widely accepted type of anesthesia in hypospadias repair (29,123-125). It is difficult to recommend regional anesthesia for pediatric penoscrotal procedures (127). The usefulness of caudal block-type anesthesia in postoperative pain control and its potential to favor complications represent a common topic. According to Routh (127) caudal block 'is not a cause of complication-according to the data- and it is not a key to success'. A restrictive regimen is preferred over the conventional intraoperative fluid regimen during hypospadias surgery (128).

Table IV summarizes the articles on anesthesia.

8. Anatomical factors

There are some anatomical factors associated with hypospadias and the severity of the malformation. Glans width, urethral plate width and shape and history of previous surgery

Table III. Summary of the articles about complications after hypospadias repair.

Author, year	Conclusions	(Refs.)
Kim *et al*, 2021 Snodgrass *et al*, 2021 Spinoit *et al*, 2021	Penile curvature appears in 25% (>30 degrees) of patients operated on hypospadias within the first 2 years.	(102) (108) (110)
Arslan *et al*, 2022	Unusual case: Combined dorsal and lateral subcoronal urethrocutaneous fistula.	(103)
Karabulut *et al*, 2022	Factors affecting glanular dehiscence: anatomical (glans width <14 mm, urethral plate width <7 mm), age (before 6 months of age and after puberty), anesthesia (caudal block).	(105)
Nguyen *et al*, 2021	Reoperation rate after distal hypospadias repair: 3.3 to 6.7%. Follow-up at least 6 years is mandatory.	(106)
Varea *et al*, 2021 Kumar *et al*, 2021	Hairy urethra or diverticulum found after hypospadias surgery using flap.	(111) (112)
Husmann, 2021	Erectile dysfunction after multiple hypospadias surgery is associated with advancing age, division of the urethral plate, prior ventral corporal grafting and repetitive internal urethrotomy for strictures.	(114)
Chapman *et al*, 2021	The consequence after urethroplasty: LUTS (lower urinary tract symptoms) related to detrusor underactivity.	(115)
Favre *et al*, 2021	The main etiological factor for urethral stricture is hypospadias.	(116)
Faraj *et al*, 2022	25% of adults presenting with bulbar strictures have a history of hypospadias repair in childhood.	(117)
Ali *et al*, 2021	Failing to correct the deficient corpus spongiosum during hypospadias surgery, may become symptomatic in adolescence.	(118)
Tack *et al*, 2021	Hypospadias repair: More reinterventions if the initial repair was performed under 12 months, urinary problems and/or suboptimal sexual functional (52.9%), suboptimal voiding (22.1%).	(119)
Godfrey, 2021	Patients with hypospadias or complete androgen insensitivity syndrome reported better mental health than patients with other 46, XY (disorders of sexual development) diagnoses.	(120)
Sembring *et al*, 2021	Preoperative testosterone administration is accompanied by decreased risk of. glandular dehiscence	(121)
Lucas-Herald *et al*, 2022	Hypospadias is associated with vascular dysfunction including hypercontractility and impaired vasodilation. Secondary endothelial dysfunction and vascular injury early in life predispose to hypertension and cardiovascular events in adulthood.	(122)

are the most important factors in hypospadias (136). In addition, the anogenital distance and penile length are diminished in children having this malformation (137). Small glans are associated with the severity of hypospadias (138). Penile curvature accompanies almost all cases of hypospadias. To objectively measure the penile curvature different degrees were defined, but it is difficult to standardize them (139,140). A paper proposes a 3D-printed penile model from a set of five pictures obtained from a lateral view (141).

Microvascular density in the prepuce is not clear which is correlated with the severity of the malformation (142). Magnetic resonance imaging is a solution to a improved view of anatomical components of the penis, even from the intrauterine stage, but we cannot imagine this procedure performed on every child presenting hypospadias (143,144). Artificial intelligence is not advanced enough to recognize and classify hypospadias (145). As another observation, 2/3 of the patients having prostatic utricle cysts present hypospadias (146).

The appetite for quantification is present in hypospadias. The Hypospadias Objective Penile Evaluation (HOPE) score, the Plate Objective Scoring Tool (POST), or the Glans-Meatus-Shaft score are proposed for an improved evaluation of hypospadias (30,147,148). Risk factors associated with complications were severe ventral curvature (the main factor), followed by urethral stricture, dehiscence, and reoperation (107).

Table V summarizes the articles about anatomical factors.

9. Genetics

Gene mutation is a proven cause for a part of these penile malformations. Table VI presents a number of cases of

Table IV. Summary of the articles about anesthesia.

Author, year	Conclusions	(Refs.)
Zhang *et al*, 2021	There are similar rates of complications between groups receiving caudal block and general anesthesia vs general anesthesia in hypospadias surgery.	(29)
Alizadeh *et al*, 2022		(123)
Koul *et al*, 2022		(124)
Adler *et al*, 2021		(125)
Osmani *et al*, 2021	It is difficult to recommend regional anesthesia for ambulatory pediatric penoscrotal procedures. It depends on the patient, anatomy, medical history, duration of surgery.	(126)
Elsonbaty *et al*, 2021	A restrictive regimen is preferred over the conventional intraoperative fluid regimen during hypospadias surgery, in terms of respiratory function and recovery.	(128)
Kandirici *et al*, 2021	Caudal block administration does not contributes to urethral fistula formation.	(129)
Sisay *et al*, 2021	A rare case report: total spinal anesthesia following caudal block.	(130)
Ponde *et al*, 2021	No difference between the success rate of the caudal block techniques: landmark guided, stimulation-guided, and ultrasound-guided; US-guided pudendal block gives more postoperative pain control.	(131)
Abdalla *et al*, 2021		(132)
Wang *et al*, 2021	Administration of 1.5 μg kg^{-1} of dexmedetomidine in the caudal block is most adequate to reduce anesthesia, and operation associated adverse events.	(133)
Hassan *et al*, 2021	Adding nalbuphine to levobupivacaine in caudal block had a longer duration for postoperative analgesia and showed more sedation time than fentanyl and dexamethasone with more stability in hemodynamics.	(134)
Karami *et al*, 2021	Caudal block can provide longer postoperative analgesia compared to penile block using rectal acetaminophen.	(135)

patients with hypospadias who had a novel mutation or a formerly mentioned one, syndromes, or complex malformations. Some genes can be associated with hypospadias in some geographical regions (such as, Algeria and China). There are only a few reviews (three) about gene complexes or syndromes that are associated with hypospadias (154-156). Genetic counseling for patients with hypospadias is mandatory, especially when hypospadias is associated with other malformations, is the conclusion of one study (157). Future studies will appear with more information and predictability and easier and more organized systems for managing genetic issues.

Table VI summarizes the articles about genetical factors.

10. Environmental factors

Maternal exposure to different chemicals can induce malformation of the penis. The most incriminated chemicals in this process are bisphenol, inorganic solvents, alkyl phenolic compounds, phthalates, benzophenones, parabens, siloxanes, pesticides or herbicides, diethylstilbestrol, cadmium, DDT, vinclozolin (fungicide), petroleum solvents and SO_2 (194-201). Some studies are more general and incriminate the air pollution, heat, or the proximity of a vineyard in the development of hypospadias (202-204).

Table VII summarizes the articles on environmental factors.

11. Endocrinological factors

In regard to endocrinological factors, two main hypotheses were identified. One is that prenatal factors: diabetes, intake of progestins, estrogens, β-blockers, assisted reproductive technology, and diethylstilbestrol (treatment in grandmothers can lead to a greater risk for hypospadias in offspring and grandsons) (207,213-217). The other is that in some penile malformations, preoperatory testosterone treatment is conducted for improved results (218-220).

Table VIII summarizes the articles about endocrinological factors.

12. Associated malformations

The best-known associated malformation with proximal hypospadias is cryptorchidism (223). Hypospadias is frequently associated with cardiac, renal and skeletal malformations (224). There is also a correlation between anorectal malformation complexity and associated urologic abnormalities (225). In addition, a number of genetic syndromes are associated with hypospadias, some of which are described in the Genetics section (section 9). A peculiarity is cases of hypospadias with disorders of sex development. Severe genital ambiguity requires complex genetic and anatomic investigation to declare the patient as a male (226-228). Other observations note that talipes, hypospadias and septal heart defects are more frequent mild defects associated with prematurity and gonadal neoplastic lesions appearing frequently together with hypospadias (229).

Table IX summarizes the articles on associated malformations.

13. Questionnaires and malformations

Some papers refer to the outcome following hypospadias surgery. Some authors call for standardization of penile

Table V. Summary of the articles about anatomical factors.

Author, year	Conclusions	(Refs.)
Zhang *et al*, 2021	Urethral plate quality is an independent factor influencing postoperative outcomes of	(29)
Abbas, 2021	hypospadias surgery. Urethral plate width has to be ≥6 mm in tubularized incised plate urethroplasty.	(140)
Galal *et al*, 2021	The urethral plate width and glandular width are not correlated with the TIP outcome. HOPE score is correlated with a wide urethral plate.	(30)
Ru *et al*, 2021	Risk factors associated with numerous reoperations: severe ventral curvature (the main factor), followed by urethral stricture, dehiscence, and primary staged repair.	(107)
Ben-David *et al*, 2021	Dorsal penile curvature associated with megameatus intact prepuce hypospadias required ventral plication.	(109)
Goel *et al*, 2021	Anatomical factors affecting the outcome of hypospadias repair: glans width (most important), urethral plate width and shape, and history of previous surgery.	(136)
Sennert *et al*, 2022	A small glans is found in about a third of distal, two-thirds in proximal, and more than 90% of perineal hypospadias.	(138)
Abbas, 2022	Patients having hypospadias had the lower scrotal base distance, anogenital distance, and penile length compared with a group of full-term healthy boys; a number of methods measure and make a degree of curvature, with strong and weak points, but no one became a standard. It is very important to have a preoperative objective quantification of curvature.	(139)
Fernandez *et al*, 2021	Standardization of penile angle with a set of 5 pictures obtained from a lateral view (0^0, 15^0, 30^0, 45^0, 60^0) at a standard distance of 75 cm results in a 3-D printed penile model with a curvature angle ranging from 10 to 90˚.	(141)
Zhao *et al*, 2021	The lower preputial microvessel density is correlated with the severity of hypospadias and early postoperative complications.	(142)
Li *et al*, 2021	Magnetic resonance imaging studies in hypospadias can present more accurate anatomical	(143)
Chaudhary *et al*, 2022	structures and the vascularization of the penis. This conduces to better preparation of surgery. This method can diagnose fetal hypospadias and evaluate the severity.	(144)
Fernandez *et al*, 2021	Artificial intelligence with digital pattern recognition used for the diagnosis and classification of hypospadias is less accurate than an experienced pediatric urologist. With an increasing number of images, the accuracy of diagnosis becomes better.	(145)
Dai *et al*, 2021	2/3 of the patients having prostatic utricle cysts present hypospadias.	(146)
Abbas, 2021	Plate Objective Scoring Tool (POST) proposes some important anatomical landmarks on the urethral plate to have an objective and accurate evaluation of this.	(147)
D'Oro *et al*, 2021	The pre-operative Glans-Meatus-Shaft Score can be altered after penile degloving and meatal displacement, resulting in a 'meatal mismatch' (20% of patients). This mismatch increase (3 times) the risk of fistula.	(148)
Gopal *et al*, 2021	Patients with and short anoscrotal distance have more chance to present severe chordee.	(149)
Yeşildal *et al*, 2021	Microvascular density in the prepuce with hypospadias is increased (also inflammation), compared to the healthy prepuce. The density of androgen and estrogen receptors are. similar	(150)
Seleim *et al*, 2021	Topographic labeling of glans and corpus spongiosum can lead to better planning of the. surgery	(151)
Abdullaev *et al*, 2021	The type of hypospadias and the length of the urethral defect are the main risk factors for recurrent fistula after primary urethrocutaneous fistulectomy.	(152)
Özbey *et al*, 2021	Long-term urethral catheterization can lead to disruption in a tear in the septum glandis and produce iatrogenic hypospadias.	(153)

appearance. The Penile Perception Score-PPS, Hypospadias Objective Score Evaluation-HOSE, International Index of Erectile Function-5-IIEF5, or Health-related quality of life (HRQoL) were conceived for that purpose (6,233). These

Table VI. Summary of the articles about genetical factors.

Genetics-Reviews		
Author, year	Conclusions	(Refs.)
Gao *et al*, 2021	There is a significant association between patients carrying MAMLD1 gene variants and micropenis, hypospadias, cryptorchidism, or split scrotum.	(154)
Ibba *et al*, 2021	DSD may be very different, with clinical variants and genetic or molecular alterations.	(155)
Nassau *et al*, 2021	Classic Klinefelter syndrome (46XXY) or mosaicism can be associated with a decrease of testosterone ambiguous genitalia, cryptorchidism, and/or hypospadias.	(156)
Genetical factors		
Fendereski *et al*, 2021	A prenatally diagnosed 46, XY DSD with a typical female phenotype caused by two heterozygous variants in LHCGR including a novel c.29_55 alteration.	(158)
Alfei *et al*, 2022	A child with BCL11B missense mutation. Hypospadias and neurologic disorders.	(159)
Li *et al*, 2021	A novel variant of SRD5A2 gene in a child featuring steroid 5α-reductase type 2 deficiency in a boy with hypospadias.	(160)
Strong *et al*, 2022	A novel MBTPS2 variant (c.766 G>A; (p.Val256Leu) is associated with Bresheck syndrome (with genotypic and phenotypic manifestation) and hypospadias.	(161)
Arsov *et al*, 2021	A novel variant in NR2F2 is associated with asplenia, immune deficiency, glandular hypospadias, and cryptorchidism.	(162)
Thomas *et al*, 2021	Two patients with Desbuquois dysplasia due to homozygous CANT1 mutations presented hypoplastic scrotum and hypospadias.	(163)
Bouhouche *et al*, 2021	A new mutation c.461G>A (p.Arg154Gln) in the short-chain dehydrogenase/reductase family 42E member 1 (SDR42E1) gene in a boy with hypospadias and ocular. malformation	(164)
Luo *et al*, 2021	A novel mutation in the HRAS gene (c.38G>T; p.Gly13Val) was detected in a patient with Schimmelpenning-Feuerstein-Mims syndrome and hypospadias.	(165)
Akramov *et al*, 2021	The WT1 gene (chr11: 32417947G>A), leads to translation termination site in the 369 codons (p.Arg369Ter, NM_024426.4) in a boy with bilateral Wilms' tumor and. scrotal hypospadias	(166)
Elghezal *et al*, 2021	HSD17B3 variants (c.239 G>A, p.R80Q) are rare causes of 46, XY DSD. Whole exome sequencing can increase diagnostic and identify genomic variants; Ring X syndrome, hypospadias with 923 Kb terminal deletion on the pseudoautosomal region 1 (PAR1) including SHOX gene followed by a duplication of 2.4 Mb.	(167)
Ravirajendran *et al*, 2021	A young adult with 45X0/46XY mixed gonadal dysgenesis who had Mullerian remnants that tend to enlarge in size over time.	(168)
Correya *et al*, 2021	Two patients presenting DSD, ambiguous genitalia with a 45XO/46XY mosaic chromosome pattern, hypospadias, Mullerian remnants, gonadal dysgenesis, streak gonad.	(169)
Chen *et al*, 2021	Mutations c.154_162delinsTCCTGTT and c.674T>A leads to3β-HSD deficiency with adrenal insufficiency and sex hormone synthesis dysfunction and hypospadias.	(170)
Saida *et al*, 2021	X-linked intellectual disability with OTUD5 gene variants: c.878A>T, p.Asn293Ile [NM_017602.4], c.1210 C>T, p.Arg404Trp and p.Arg404Trp.	(171)
Çiftci *et al*, 2022	A case of 46XY patient with female phenotype who had a variation in the HSD17B3 gene: c.673_1G>C homozygous class 2 (splice site) variation in intron 9.	(172)
Laan *et al*, 2021	Partial gonadal dysgenesis in 46XY patients with NR5A1 c.991-1G > C splice-site variants: OTX2 p.P134R or PROP1 c.301_302delAG.	(173)
Gerber *et al*, 2021	Robinow syndrome is a rare, genetic disorder. Boys may have genitourinary atypicality, among them hypospadias in 5/8 patients.	(174)
Sheppard *et al*, 2021	Heterozygous recurrent HNF4A variant p.Arg85Trp causes Fanconi renotubular syndrome 4, diabetes, Fanconi Bickel syndrome with colobomas and hypospadias.	(175)

Table VI. Continued.

Author, year	Conclusions	(Refs.)
Genetical factors		
Tripolszki *et al*, 2021	X-linked syndrome in 13 males of a family with a missense variant in the OTUD5 gene. Neurodevelopmental problems, congenital heart defects, and hypospadias were noted.	(176)
Hage *et al*, 2021	A novel androgen receptor gene mutation in two patients with mild insensitivity syndrome. It was found a novel missense mutation, Ala699Thr, in exon 4 within the ligand-binding domain.	(177)
Basa *et al*, 2021	Pathogenic Aristaless novel gene-variant C1010_1013dupGCTA; p.Tyr338 in a lissen cephaly boy with ambiguous genitalia.	(178)
Genetic research on a population or on hospitalized patients		
Li *et al*, 2021	SRD5A2 and AR genes are two top candidate genes associated with 46, XY hypospadias in Chinese patients.	(160)
Kherouatou-Chaoui *et al*, 2021	It was found the absence of SRY and NR5A1 gene mutation in Algerian children. with DSD	(179)
Chen *et al*, 2021	An important link was found between rs12458 (3'-UTR of GATA4) and susceptibility to hypospadias.	(180)
Wong *et al*, 2022	Children affected by 45, X/46, XY mosaicism have a wide spectrum in their phenotypes.	(181)
Deng *et al*, 2021	GREM1 is associated with susceptibility to hypospadias in the European population. GREM1 risk allele rs3743104[G] increases hypospadias susceptibility among the southern Han population.	(182)
Siregar *et al*, 2021	ESR1 gene polymorphisms (PvuII, XbaI, and SNP 12) were found in hypospadias patients and there are correlate with the severity of hypospadias.	(183)
Genetic counseling		
Nordenskjöld *et al*, 2021	Genetic counseling for patients with hypospadias is mandatory, especially when hypospadias is associated with other malformations. The risk of low fertility is a reality.	(157)
Saraç *et al*, 2021	Genes involved in the sonic hedgehog homolog pathway might play a role in the etiology of hypospadias.	(184)
Tenenbaum-Rakover *et al*, 2021	In DSD, 78% of our patients indicate a major role for whole-exome sequencing and its role in the diagnosis and management of the cases.	(185)
Ea *et al*, 2021	Next-generation sequencing reveals different forms of DSD (including hypospadias). It is important to have a follow-up and medical counseling in future.	(186)
Genetical syndromes and malformations		
Schmidt *et al*, 2022	Variants in the transcription of the factor TP63 have been linked to several autosomal dominantly inherited malformations. Hypospadias is one of these malformations.	(187)
Ding *et al*, 2021	Noonan syndrome (frequently with hypospadias and cryptorchidism), is associated with PTPN11 variation, and SOS2 gene variation more often than previously reported.	(188)
Lourenço *et al*, 2021	An aberrant right subclavian artery may be associated with mosaicism 45, X [13]/46, X,e(X) (p22.1q22.1) and in some cases with hypospadias.	(189)
Konishi *et al*, 2021	5α-reductase type 2 deficiency may lead to ambiguous phenotypes.	(190)
Rjiba *et al*, 2021	In Wolf-Hirschhorn syndrome we find a partial deletion of the short arm of chromosome 4. MSX1 gene absence might be responsible for the hypospadias phenotype in these children.	(191)
Genetical and histological analyses		
Yuri *et al*, 2021	The expression of mRNA vascular endothelial growth factor in hypospadias patients does not affect the severity of hypospadias (dartos).	(192)

Table VI. Continued.

Genetical and histological analyses		
Author, year	Conclusions	(Refs.)
Kong *et al*, 2021	The expression of the Mafb gene and protein in the foreskin of children with hypospadias is lower than that in the normal foreskin.	(193)

Table VII. Summary of the articles about environmental factors.

Author, year	Conclusions	(Refs.)
Spinder *et al*, 2021	Maternal exposure to Bisphenol A, organic solvents/alkyl phenolic compounds and	(194)
Rodprasert *et al*, 2021	phthalates/benzophenones/parabens/siloxanes, pesticides in early pregnancy is	(195)
Mesquita *et al*, 2021	associated with urogenital anomalies in the offspring.	(205)
Mattiske *et al*, 2021	Genistein, Bisphenol A (BPA), Phthalates, Parabens, flame retardants, solvents, agricultural chemicals, Atrazine (herbicide), DDT, and Vinclozolin (fungicide) can interfere with androgen and estrogen levels during the development and result hypospadias.	(196)
Laws *et al*, 2021	Plasticizers (bisphenols and phthalates), personal care products (parabens),	(197)
Stukenborg *et al*, 2021	environmental contaminants (polychlorinated biphenyls), herbicides or	(198)
Giovanni *et al*, 2022	pesticides, cadmium, conduct to male disorders: infertility, cryptorchidism, hypospadias, and testicular cancer. We have to focus on prenatal exposure to mild analgesics: acetaminophen (more involved) and Ibuprofen (less involved).	(199)
Wu *et al*, 2022	Maternal exposure to pesticides, phthalates, bisphenol A, and polychlorinated	(200)
Gaspari *et al*, 2021	biphenyls are associated with hypospadias and micropenis in offspring. They have transgenerational effects with long-term effect.	(201)
Huang *et al*, 2021	Air pollution during pregnancy was associated with the occurrence of hypospadias, but conclusions have been inconsistent. Some ethnic groups may present a type of such malformation.	(202)
Xing *et al*, 2021	Air pollution and risk of hypospadias in offspring: there is an effect of $PM_{2.5}$ exposure on hypospadias risk.	(203)
Bougnères *et al*, 2021	The residence of pregnant mothers close to vineyards was statistically linked with the risk of hypospadias in children.	(204)
Soyer-Gobillard *et al*, 2021	Prenatal exposure to Diethylstilbestrol produced multigenerational phenotypic (hypospadias endometriosis) and psychiatric disorders.	(206)
Zhang ZC *et al*, 2021	Dibutyl phthalate is an endocrine disruptor. It has anti-androgenic effects and a weak estrogenic effects. Lower doses cause more adverse effects than the highest dose.	(207)
Zhang S *et al*, 2021	Maternal exposure to SO2 during the 3 months before and the first and second months after conception may increase the risk of hypospadias in offspring.	(208)
Rouget *et al*, 2021	An association between petroleum solvents and hypospadias has been observed.	(209)
Haghighi *et al*, 2021	The appearance of hypospadias is linked to heat exposure. Effects increased with the duration and intensity of heat exposure.	(210)
Gadagbui *et al*, 2021	Procymidone as an endocrine disrupting chemical can produce hypospadias but is not very suggestive for other malformations.	(211)
Lin *et al*, 2021	There is a modest association between prenatal PM2.5 (fine particulate matter) exposure during 1 month before pregnancy or within the first trimester and the risk of hypospadias in offspring.	(212)

scores are different from the point of view of patients, parents, or surgeons so there is no standard yet. Curvature and shortening are the anatomical modifications most perceived by the patients (234). Voiding, erectile problems, social interaction

Table VIII. Summary of the articles about endocrinological factors.

Author, year	Conclusions	(Refs.)
Zhan ZC, 2021	Prenatal and/or gestational factors (diabetes), intake of different treatments during	(207)
Akay *et al*, 2021	pregnancy (progestins, estrogens, β-blockers), assisted reproductive technology	(213)
Chung *et al*, 2021	and diethylstilbestrol treatment in grandmothers can lead to a greater risk for	(214)
Baskin *et al*, 2021	hypospadias in offspring and grandsons.	(215)
Wu *et al*, 2021		(216)
Schraw *et al*, 2021		(217)
Liu *et al*, 2021	Testosterone treatment in children with hypospadias, especially those with a	(218)
Khokar *et al*, 2021	5α-reductase deficiency, can alter its degree and lead to a greater success for the operation.	(221)
Li *et al*, 2021	Preoperative androgen stimulation is used in proximal hypospadias or small glans	(219)
Chukwubuike *et al*, 2021	size. It appears it does not affect the operative outcome, but it is not certain.	(222)
Concepción *et al*, 2021	Boy with partial androgen insensitivity syndrome (having hypospadias and cryptorchidy), required testosterone therapy and genitoplasty.	(220)

Table IX. Summary of the articles about associated malformations.

Author, year	Conclusions	(Refs.)
D'Oro *et al*, 2021	Patients with proximal hypospadias present a higher risk of acquired. cryptorchidism	(223)
Ludorf *et al*, 2021	Hypospadias is most frequently associated with cardiac, renal, and skeletal malformations. Hypospadias in combination with eye defects did not include defects in other organ systems.	(224)
Fuchs *et al*, 2021	There is a correlation between anorectal malformation complexity and associated urologic abnormalities.	(225)
De Jesus *et al*, 2021	Cases of hypospadias in the disorder of sex development (DSD) associated with	(226)
Nelwan *et al*, 2021	ovotestis, severe genital ambiguity, and the child was declared male after	(227)
Ashfaq *et al*, 2021	elaborate analysis or an apparent male with infertility who presented 46 XX karyotype.	(228)
Álvarez-Álvarez *et al*, 2021	Cases of hypospadias associated with Dandy-Walker malformation (75), bifid	(230)
Viet Nguyen *et al*, 2021	phallus (77), dorsal penile curvature with megameatus (136), Wolf-Hirschhorn	(231)
Çelik *et al*, 2021	syndrome (262).	(232)

and psychological issues are the functional problems after surgery (233,235).

Table X summarizes the articles about questionnaires and malformations.

14. Management

For most families, a boy having hypospadias is a psychological trauma. Usually, parents do not know about this malformation and have to be informed, and this is not always, in terms of time and explanation, what they expect. The need for reintervention is perceived in the majority of cases as a trauma for patients and parents (3,38). An article claims that hypospadias and neurologic impairment may share common etiologic factors, thus every patient with hypospadias should be evaluated for neurodevelopmental status (243). Timing for complex malformations has to be considered individually in every case. Delayed surgery in children with hypospadias is also determined by the economy of the area where the family lives and the educational level of the parents (240).

In a hospital register, it is not easy to classify hypospadias properly, although there are algorithms for identification (248). Another question is: 'What are the specialties of the surgeons who are managing these cases?' Usually, they are pediatric surgeons or pediatric urologists (depending on the country) (249). Regardless of the specialty, the repair of hypospadias requires an experienced doctor. The learning curve seems quite long; surgeons are considered experienced in the field after treating a minimum of 50 cases, supervised by an experienced surgeon (7). When the child becomes an adult, it is better to be managed by urologists trained in genitourinary reconstructive surgery (250). It is

Table X. Summary of the articles about questionnaires and malformations.

Author, year	Conclusions	(Refs.)
Snodgrass *et al*, 2021	Parents of boys with hypospadias: the majority never previously heard of it, wondered if they are to blame for it and are concerned about future boys. A part of the report is that doctors did not spend enough time discussing these problems.	(3)
van Engelen *et al*, 2021	A substantial number of parents report some form of decisional regret regarding the elective surgery for hypospadias in their child.	(4)
Costa *et al*, 2021	Surgeons seem more concerned about the cosmetic part of hypospadias surgery than parents. Photography appears to be suitable for documenting corrections of hypospadias regarding penile curvature, and postoperative cosmetic results.	(5)
Ceccarelli *et al*, 2021	Three questionnaires: The Penile Perception Score-PPS, the Hypospadias Objective Score Evaluation-HOSE, and the International Index of Erectile Function-5-IIEF5 to patients, parents, and surgeons. The results are different, so there is a need for standardization.	(6)
Hismatsu *et al*, 2021	The learning curve in proximal hypospadias repair appears after 50 cases, supervised by an experienced surgeon.	(7)
Ludovica *et al*, 2021	Self-reported outcomes in adolescent patients who had TIP repair are similar to the control group. Preputial reconstruction or circumcision did not affect the outcome.	(31)
Bhatia *et al*, 2021	Health-related quality of life (HRQoL): penile appearance, voiding, social interaction, sexual health and psychological or behavioral function, have to serve as a guide for future assessments. Patients are usually focused on penile appearance.	(233)
Hoare *et al*, 2021	Penile modifications after urethroplasty is perceived by individuals, especially in curvature and shortening.	(234)
Chang *et al*, 2021	A significant percentage of adolescents or young adults operated in childhood with hypospadias, present aesthetic complaints (majority) or functional problems (fistula, spaying).	(236)
Sinatti *et al*, 2021 Hermosa *et al*, 2021 Mallenahalli *et al*, 2021	Psychosexual satisfaction of adults who had hypospadias surgery demonstrates equal satisfaction rates to those in control group. Interventions on the penile urethra, long panurethral urethroplasties, and reinterventions are associated with greater risks. The functional benefit of non-transecting approaches and grafting techniques on bulbar urethra remains controversial.	(237) (238) (239)
Zhang *et al*, 2021	Delayed surgery in children with hypospadias is determined by the economy of the area where the family lives, the educational level of the parents, and the location of the urethral opening.	(240)
Bennecke *et al*, 2021	From patients' perspective, early genital surgery in DSD is more accepted, but every case has its complexity, so it cannot be applied as a rule.	(241)
Bangalore *et al*, 2021	The patient's family is encouraged to make individualized treatment guided by shared decision.	(242)
Cakmak *et al*, 2022	Hypospadias and neurologic impairment may share common etiologic factors, thus every patient with hypospadias should be evaluated for neurodevelopmental status.	(243)
van de Grift *et al*, 2022	The majority of patients with DSD, who had a history of surgery were neutral to satisfied with the appearance and function after masculinizing operations.	(244)
Gul *et al*, 2021	Sexual functions and fertility outcomes after hypospadias repair may be affected in some patients.	(245)
Guner *et al*, 2021 Buyukunal *et al*, 2021	Hypospadias was one of the early reported malformations in the history of medicine, but very little specific urogenital disease information is mentioned in ancient age sanctuary medicine. Surgical techniques used now were elaborated in the 20th century.	(246) (247)

important to inform general practitioners, and pediatricians about the management of hypospadias, as it seems that a number of them do have not adequate knowledge about the condition (251).

Table XI. Summary of the articles about hypospadias management.

Author, year	Conclusions	(Refs.)
Baker *et al*, 2021	Methods for classifying distal hypospadias and other urologic problems in registers, present a high risk for misclassification.	(248)
Maier *et al*, 2021	In Germany, hypospadias surgery has shown a relevant shift towards pediatric surgery, from pediatric urology.	(249)
Scarberry *et al*, 2021	Patients who become adults are better managed by urologists trained in genitourinary reconstruction.	(250)
Mahalik *et al*, 2021	Indian questionary among pediatricians: about half of them know what to do and recommend to a patient with hypospadias.	(251)
Kharbanda *et al*, 2021	Algorithms can identify infants with selected birth defects using automated health care data with reasonable accuracy.	(252)

Table XII. Summary of the articles about biological materials in hypospadias repair.

Author, year	Conclusions	(Refs.)
Wu *et al*, 2021	Acellular dermal matrix graft is a good material for ventral lengthening of the penis, comparable with tunica vaginalis.	(253)
Singh *et al*, 2021	A review of tissue sealants: fibrin glue, cyanoacrylate glue, Bio Glue, and cryocalcium glue. They can reduce complications (fistula, cutaneous lesions), but they remain inconclusive.	(254)
Wang *et al*, 2021	Acellular dermal matrix modified with Collagen-Binding VEGF was successfully used in the urethral reconstruction of a dog without severe inflammation.	(255)
Morgante *et al*, 2021	Two acellular matrix grafts for tissue bed for surgical repair were compared: full-thickness porcine acellular bladder matrix and commercially-sourced cross-linked acellular matrix from the porcine dermis (Permacol™). The two were conducive to good results.	(256)
Tawfeek *et al*, 2021	The application of cyanoacrylate during fistula repair is feasible and safe.	(257)
Shenoy *et al*, 2021	Fibrin sealant, applied over the urethroplasty suture represents a good cover and improves the outcome in patients with hypospadias.	(258)

Table XI summarizes the articles on hypospadias management.

15. Biological materials

Biological engineering materials and products are becoming increasingly popular in hypospadias repair and the present study enumerated some of them which were used in urethroplasties. Acellular dermal matrix grafts (with Collagen-Binding VEGF), harvested from the bladder or derm were successfully used in the urethral reconstruction and authors claim that the results were comparable with tunica vaginalis (253). Tissue sealants such as fibrin glue, cyanoacrylate glue, Bio Glue, and cryocalcium glue were used to reduce fistula-related complications (254).

Table XII summarizes the articles about biological materials in hypospadias repair.

16. Animal models

Experiments on animals are rare, poorly reported, less detailed and not reproducible (as a review found) (259). A single urethral reconstruction is reported in a rabbit model. It used a decellularized intestinal submucosa, seeded with urothelial cells (260). Specific genes were discovered and involved in hypospadias formation in rats and mice (261-264). Prenatal atrazine and vinclozolin exposure can affect penile and testicular development (265).

Table XIII summarizes the articles about animal models.

17. Retrospective studies of centers

Table XIV summarizes the articles about retrospective studies of centers.

18. Social media

On social media (Facebook, Twitter and others), the problem of hypospadias is debated, but much of the shared content does not have supporting evidence and is not affiliated with medical journals, hospitals, or academic institutions. For parents with insufficient medical knowledge, it could be difficult to identify whether the articles shared on social media

Table XIII. Summary of the articles about animal models.

Author, year	Conclusions	(Refs.)
Abbas *et al*, 2021	Urethral repair experiments on animals are poorly reported, less detailed and are not reproducible.	(259,266)
Amesty *et al*, 2021	Rabbit urethral defect: neourethra is created by seeding autologous urothelial cells by bladder washing on a decellularized intestinal submucosa matrix (Biodesign® Cook-Biotech®). Cell-seeded transplants are superior to nonseeded.	(260)
Palermo *et al*, 2021	A putative pathway network for a male rat, sustained expression of Coup-tfII and hypospadias.	(261)
Alcantara *et al*, 2021	Wnt5a contributes to urethral tube formation in mice.	(262)
Xiang *et al*, 2021	c-Fos overexpression might contribute to hypospadias (rats and humans) and	(263)
Feng *et al*, 2021	NONRATT008453.2 may have an influence on autophagy in the fibroblasts of the genital tubercle in dibutyl phthalate-induced hypospadias in rats.	(264)
Yu *et al*, 2021	Maternal vinclozolin exposure can lead to penile and testicular damage (via miR132,	(265)
Tan *et al*, 2021	miR195a) in the offspring. Prenatal atrazine exposure can induce hypospadias and cryptorchidism in mice.	(267)
Tokat *et al*, 2021	Intraurethral erythropoietin administration facilitates wound healing after hypospadias correction in rats.	(268)
Gulburun *et al*, 2021	Hydrogen-rich saline solution reduces inflammation on the flap tissue in the hypospadias model in rats.	(269)

Table XIV. Summary of the articles about retrospective studies of centers.

Author, year	Conclusions	(Refs.)
Kaefer *et al*, 2021	A great lesson and the experience of a top surgeon regarding hypospadias.	(2)
Fruntelată *et al*, 2021	Overview of center regarding hypospadias from Romania, Afghanistan, Kenya,	(270)
Raheem *et al*, 2021	Pakistan or Saudi Arabia in time of COVID.	(271)
Jurat *et al*, 2021, 2021		(272)
Irene *et al*, 2021		(273)
Khan *et al*, 2021		(274)
Ashwin *et al*, 2021	A lifelong view and review of staged and multiple urological surgeries or the	(275)
Wiener *et al*, 2021	treatment of strictures	(276)
Ács *et al*, 2021	A database of the Hungarian congenital abnormalities. Hypospadias is number four.	(277)
Benavides *et al*, 2022	Birth defects prevalence in Texas, where hypospadias is less prevalent in rural counties compared with urban counties.	(278)
Arulanandam *et al*, 2021	In Quebec, the compliance rates, regarding hypospadias are inadequate and need improvement.	(279)

are a reliable resource for health. YouTube videos present different surgical treatments for this malformation, but the majority of the content is non-medical and may lead to health misinformation (280-282).

Table XV summarizes the articles about social media.

19. Others

Table XVI summarizes the articles about bibliometrics, small gestational age, neoplasm and fertility.

20. Discussion

As can be seen, hundreds of papers are written every year about hypospadias, referring to all aspects of the pathology. 2021 was mostly a year of accumulation, with a number of papers comparing and hoping for new surgical techniques with improved outcomes, clarifying the relevant anatomical, etiological and genetic factors, assuming the complications, and describing solutions to prevent or treat them. As a limitation of the present study, quality assessment of the included articles was not performed.

Table XV. Summary of the articles about social media.

Author, year	Conclusions	(Refs.)
Karabay *et al*, 2021 Jones *et al*, 2022	There is a scarcity of high-quality videos on YouTube describing distal hypospadias repair techniques and, further, their quality regarding educational content seems to be unsatisfactory.	(280) (281)
Cheng *et al*, 2022	Most interesting pediatric urologic issues (including hypospadias), debated on social media (Facebook, Twitter) are debated strongly, but not very relevant.	(282)

Table XVI. Others.

Bibliometrics		
Author, year	Conclusions	(Refs.)
Ghidini *et al*, 2022	The top-cited articles were dispersed among 27 journals of different areas with a median impact factor of 2.676. Current scientific literature deals with congenital anomalies, more specifically with obstructive uropathies and hypospadias. In the last decade, one of the most relevant innovations in pediatric urology was the introduction of robotic surgery.	(283)
Matta *et al*, 2021	The list of top 100 most cited articles in pediatric urology is an important resource for clinicians and trainees to understand the body of knowledge and trajectory of this field, charting the evolution of the field and highlighting areas of a potential investigation.	(284)
Dogan *et al*, 2021	Between 1980 and 2018, there were 1940 articles about hypospadias, the USA was the top country that contributed to the literature and the top active 3 journals were the Journal of Urology, Journal of Pediatric Urology, and Urology.	(285)
Small gestational age		
Rittler *et al*, 2021	Talipes, hypospadias, and septal heart defects are more frequent mild defects significantly associated with prematurity.	(229)
Braga *et al*, 2022	Children born small for gestational age present a high frequency of hypospadias. Cases were studied genetically, but it was not identified the cause. They conclude that multifactorial causes or unidentified epigenetic defects produce the malformation.	(286)
Neoplasm, fertility		
Huilin *et al*, 2021	A series of cases with gonadal neoplastic lesions associated with hypospadias Men with	(287)
Philips *et al*, 2021	hypospadias do not present impaired semen quality using dizygotic twinning as an epidemiological indicator.	(288)

According to the findings of the present study, it is possible to highlight the following ideas considering that these might have direct clinical significance: Promising modifications in proximal hypospadias repair were presented and transverse preputial island flap urethroplasty with incised urethral diversion appeared a superior option compared with trans-urethral diversion (8). Two-stage urethroplasty had improved results compared with one-stage surgery (10,12,16,35,36). Tubed pedicled preputial island flap, Duckett's procedure, was associated with a high complication rate (44). Predictors of a successful outcome of tubularized incised plate (TIP) repair in cases of distal hypospadias were described by different authors (53,86). Dorsal inlay graft urethroplasty was considered a superior technique compared with onlay preputial flap (LOF) (19). With the exception of the long-term outcomes in cosmetic and functional evaluation, Mathieu incised plate technique had improved outcomes compared with the TIP technique (63). For the treatment of congenital ventral penile curvatures, dorsal plication was defined as a relatively simple and successful method with low risks (34). There were no differences in outcomes between pre-pubertal and post-pubertal boys after the correction of penile curvature using corporal plication (70). In order to decrease the rate of complications new dressing techniques, and topical agents were mentioned along the hyperbaric oxygen therapy (88,89,96,97,99). Perioperative prophylactic

antibiotics appeared not to reduce the possibility of infections (101). A total of 25% of adults presenting with bulbar strictures had a hypospadias surgery in childhood (117). Penile curvature could appear in 25% of patients within the first 2 years (102,108,110). According to postoperative care, surgeons appear more concerned about the cosmesis than do the parents. Photo documentation of cosmesis (and to evaluate penile curvature) is appropriate at present (5). Self-reported outcomes in adolescent patients with TIP repair were similar to those in a control group (31). Delayed surgery could be determined by the region's economy, the parent's educational level and the urethral opening site (29). There were noteworthy pediatric urologic issues, including hypospadias, on social media and they are debated, but most of them are not very relevant. There is a scarcity of high-quality videos on YouTube describing hypospadias repair techniques, and their quality regarding educational content appears unsatisfactory (280-282).

The novelty of the present study consisted of the lack of similar analyses. To the best of the authors' knowledge, no similarly conceptualized studies have been previously performed in this research field. As a scoping review, the present study represented a well-structured and reproducible mapping of the literature. It aimed to define and clarify key concepts, theories, the most important results and achievements, and to present them in a transparent way, highlighting areas where researchers could identify gaps in the current literature that may require further inquiry. The present study presented sources of evidence that inform practice in the field, eases further investigations and saves time and resources. Hypospadias research in 2021 represents a very complex field. A comprehensive scoping review such as the present constitutes essential information for every pediatric surgeon, urologist, and specialist in this field.

21. Conclusion

According to the papers published in 2021, promising modifications of existing surgical techniques were presented with improved outcomes for the proximal and distal types of hypospadias forms. The present study highlighted and clarified the presented relevant anatomical, etiological and genetic factors. For an improved understanding of the aspects of peri- and postoperative management of hypospadias the antibiotherapy, analgesia, dressing techniques and the future use of novel bioengineering agents to prevent, reduce or treat the occurring complications, were also discussed.

Acknowledgments

Not applicable.

Funding

No funding was received.

Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

HG and ZB were responsible for conceptualization and methodology. ZB was responsible for software. HG, ZB, ED and ZD were responsible for validation. ZB was responsible for formal analysis. HG was responsible for investigation. ED and ZD were responsible for data curation. HG wrote the original draft. HG, ZB, ED and ZD wrote, reviewed and edited the manuscript. ZB was responsible for visualization and supervision. HG was responsible for project administration. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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