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Ana Carolina Freitas Ribeiro

Revisão sistemática: Existe uma relação entre restrição de crescimento fetal, de causa placentária, e hipospadia em gravidezes únicas?

Systematic review: Is there a connection between the fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies?

MARÇO, 2023

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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Systematic review: Is there a connection between the fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies?

ORIENTADOR

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Systematic review: Is there a connection between the fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies?

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Abstract

Introduction: The origin of hypospadias is uncertain and thought to involve genetic and environmental factors. Our aim is to comprehend the correlation between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies.

Material and Methods: We performed a systematic review searching on PubMed, Web of Science, and Scopus databases. Articles evaluating the association between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies were included. A total of 12 studies were included, and their relevant data were extracted and qualitatively analyzed. The risk of bias was measured using the NIH Study Quality Assessment Tool.

Results: Seven articles reported that fetal growth restriction and small for gestational age are important risk factors for the development of hypospadias. Four studies concluded that low birth weight is associated with the higher prevalence of hypospadias. Only one study found no significant differences between the birth weight of boys with and without hypospadias. In four studies anatomopathological evaluations of the placenta was performed, and in all signs of placenta dysfunction were more frequent in infants with hypospadias. Five studies evaluated the weight of placenta, and concluded that weight of placenta of boys with hypospadias was lower than weight of placenta of healthy boys. Two studies found preeclampsia as a risk factor for hypospadias.

Discussion: Our results highlight fetal growth restriction as a potential cause of increased prevalence of hypospadias. Placental dysfunction may be the underlying mechanism, considering that children with hypospadias, in addition to having lower birth weight, also had placenta with lower weight and more anomalies. The major limitations of our review are the differences in methodology of the studies included, most of them conducted several years ago.

Conclusion: Our systematic review confirms an association between fetal growth restriction and hypospadias.

Keywords: Hypospadias; Small for gestational age; Intrauterine growth restriction; Fetal growth restriction; Low birth weight; Placental insufficiency.

Introduction

Hypospadias is a male congenital anomaly, characterized as a ventral position of the urethral orifice caused by an incomplete development of the urethra between the 7th and 14th week of gestation [1,2,3]. This genital defect is increasing worldwide [4] and the prevalence ranges differ globally, from low in Asian countries (0.06/1000) to very high in Northern European countries (46.4/1000) [5].

There are various phenotypes classified according to the position of the urethra: anterior (urethral opening at the glans or corona), middle (urethral orifice is on the shaft of the penis) and posterior (urethra emerge in the penoscrotal region, scrotum or perineum) [6,7]. Surgical repair is the only treatment, but expectant management also can be a choice, in case of minimal anomalies [7].

The etiology behind the development of hypospadias is still unknown. Evidence suggests that it is multifactorial, involving both genetic and environmental factors [8,9, 10]. Maternal factors as maternal age, primiparity, obesity, fertility treatments and fetal factors as low birth weight, higher placenta-to-fetal ratio, fetal growth restriction (FGR) have been associated with hypospadias [8,11].

Among all the risk factors that have been implicated in hypospadias, being small for gestational age (SGA) is thought to be one of the most important, and is a topic explored by several studies. The main explanatory hypothesis is that deficient secretion of human chorionic gonadotropin (hCG) may play an important role in the origin of hypospadias, since being small for gestational age is often a result of placental insufficiency [3,9,12].

According to several studies, boys with hypospadias had lower placental weight [3,13,14,15,16]. In fact, the synthesis of testosterone by Leydig cells in the fetal testis, during the first trimester, is stimulated by hCG from the placenta, and an insufficient androgen production may affect masculinization, urethral fusion, and testicular descent [17].

The aim of our study is to understand the association between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies.

Methods

We performed a systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance [18]. The literature search was performed in February 2022 in three databases - PubMed, Scopus, and Web of Science, using the query: (Hypospadias) AND (Small for gestational age OR Intrauterine growth retardation OR Intrauterine growth restriction OR Fetal growth restriction OR Fetal growth retardation OR Low birth weight).

We included observational and human studies that evaluated the association between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies. Animal studies, case reports or systematic reviews, and studies in which the cause of fetal growth restriction was genetics were excluded. Only studies in English and Portuguese were included. There was no publication date restriction.

Although we defined from the beginning that only studies with single pregnancies in cases would be included, Hashimoto *et al.* [19] was an exception. Despite having four cases of twins, it was included in this systematic review. The existence of a table in the article with patient background data allowed to select and analyze only single pregnancies, not being biased by the other cases.

After the removal of the duplicates, the selection of the articles obtained from databases were done independently by two authors. This step was based on the titles and abstracts analyses. Any disagreement in the inclusion of the studies was resolved by consensus. Afterwards, one of the reviewers had read the full-text articles assessed for eligibility.

The data extraction from the included studies was performed manually by one of the authors. The data extracted (authors, publication year, the country where the study was performed, study design, objective, sample, control group, results, and conclusions) was introduced into a table. Considering the nature of the data, only qualitative analysis will be performed.

The risk of bias was measured using the NIH Study Quality Assessment Tool, NIH quality assessment tool for observational cohort and cross-sectional studies and NIH quality assessment tool for case-control studies. [20] The quality of the article was rated as Poor symbolized by "0", Fair designated by "i", and Good indicated by "ii".

Results

The result of the database searching was a total of 963 articles, 207 on PubMed, 551 on Scopus, and 205 on Web of Science. After removing the 219 duplicates, the selection started with the title and abstract analysis, which resulted in the inclusion of 49 articles and the exclusion of 695 which did not meet the eligibility criteria. Thereafter, a full text analysis was conducted, and leaving a total of 12 articles that were included in this systematic review. The entire search and selection strategy are described in Figure 1, using the PRISMA 2020 flow diagram [18]. The relevant data of the studies included are registered in Table 1.

Of the articles included, ten were cohort studies, and the other two were a cross-sectional study and a case control study. The studies were published between 1986 and 2019 and were conducted in Europe (5 studies), Asia (4 studies), and America (3 studies).

The assessment of the risk of bias for cohort and cross-sectional studies is present in Table 2, and for case-control study in Table 3. Regarding cohort and cross-sectional studies, seven articles may have confounding bias, as there had not evidence about measure and adjust of key potential confounding variables. Almost every article may contain performance bias, because they were not doubled blinded, only one cohort article ensured study blindness. Detection bias could only be assessed in seven studies. Therefore, ten articles were rated as “Fair”, and one article as “Poor”. Concerning case-control study, it was not possible to evaluate performance bias, because there was no information about the study blinding. Neither confounding bias nor detection bias were observed. Accordingly, the article was classified as “Good”.

One article [21] supported the idea that the prevalence of hypospadias is rising. Nissen *et al.* [21] concluded that during the period of 2000-2009 the prevalence of hypospadias was higher when compared to the period of 1986-1999 (23.7 per 10 000 births vs 12.0 per 10 000 births, $p<0.001$).

Of the 12 articles included, in seven [16,19,21-25] weight for gestational age was assessed, using the definition based in percentile [19,21-24] or using the standard deviation (SD) score for gestational age [16,25]. This allowed the identification of fetal growth restriction and small for gestational age as important risk factors for the development of the hypospadias. Moreover, Nissen *et al.* [21] noted that the more severe the growth restriction, the more possibly the anomaly will occur, affirming that low birth weight is related to a high prevalence of hypospadias, with greater than a three-fold higher risk for very low birth weight (VLBW) infants.

Four studies solely evaluated the mean birth weight, without considering gestational age [26-29]. In three of them the authors found a correlation between low birth weight and hypospadias [26-28]. In the study performed by Hsieh *et al.* [29] no significant differences in birth weight were found between boys with and without hypospadias.

Boisen *et al.* [13] assessed both birth weight and weight for gestational age expressed as percentage deviation from the expected mean. Despite boys with hypospadias had lower mean weight compared with healthy boys [-5.00% (11.3) vs. -0.59% (12.4), p= 0.030)], only one case was small for

gestational age (weight for gestational age = -42.54%) while the rest had appropriate weight for gestational age (range -21.09 to 24.18).

In four studies anatomopathological evaluations of the placenta was performed [16,19,22,23]. In all, placental insufficiency was identified, which allowed supporting the idea that growth restriction is caused by alterations in placenta. Fujimoto *et al.* [16] found abnormalities in placenta such as infarction, calcifications, and degenerative changes more frequently in infants with hypospadias. Hashimoto *et al.* [19] concluded that children with FGR are more likely to develop hypospadias, and the main cause of it is placental dysfunction, caused by severe placental infarction or abnormal umbilical cord.

Five studies [13,16,19,22,23] evaluated the placental weight, and all of them concluded that low placental weight is related to the development of hypospadias. In the study of Boisen *et al.* [13] placenta weight of boys with hypospadias was lower than the placenta weight of healthy boys, which is another supportive point for placental insufficiency as restriction etiology. Fujimoto *et al.* [16] showed that placenta-to-fetal weight ratio (0.323 ± 0.07 vs. 0.229 ± 0.03, $p < 0.01$) and placental weight–to–fetal age ratio (14.10 ± 1.84 vs. 8.53 ± 2.06, $p < 0.01$) were significantly higher in boys with hypospadias compared with those who did not have the condition. Hashimoto *et al.* [19] performed a placental study of five of the cases included in the study, and in three of them the placental weight was lower than the 10th percentile. Chen *et al.* [22] found that low placental weight was more prevalent in boys with hypospadias compared to boys without hypospadias (adjusted OR = 2.7; 95% CI: 1.3-5.9).

In two studies [22,26], preeclampsia was identified as risk factors for hypospadias, which also suggest placental insufficiency as a possible cause of fetal growth restriction. Kovalenko *et al.* [26] concluded that children who born to mothers with preeclampsia exhibited increased risk for hypospadias (OR = 1.65; 95% CI 1.03–2.66).

In one study [24], familiar history of urological anomalies was also evaluated as a possible risk factor, and a previous sibling with hypospadias was associated with the development of hypospadias. After adjusting for a previous sibling with hypospadias, SGA (1.8, 95% CI 1.03-3.1) and a previous sibling with hypospadias (12.85, 95% CI 9.2-18.12) remained as significant risk factors.

Discussion

This systematic review corroborates the association between fetal growth restriction and increased likelihood of developing hypospadias. It is hypothesized that hypospadias is caused by placental dysfunction, which results in a deficient secretion of hCG. Shinar *et al.* [30] clarified this theory showing that low levels of placental growth factor (PlGF), a vascular endothelial growth factor produced by the syncytiotrophoblast, were associated with an estimated fetal weight below 5th percentile compared with normal levels of PlGF (53% vs 73.8%, $p<0.01$). Additionally, maternal vascular malperfusion of the placenta was more common in pregnancies with low PlGF (85.7% vs 39.7%, $p < 0.0001$) [30]. So, as already concluded placental insufficiency is associated with SGA infants, who, have a higher prevalence of hypospadias [16,19]. Actually, Melamed *et al.* [31] showed that SGA was associated with an increased risk of placental pathology (aRR 1.60 [95% CI: 1.10-2.31]), namely maternal vascular malperfusion, chronic villitis, and fetal vascular malperfusion.

Furthermore, the association between placental weight and hypospadias also supports the hypothesis of placental insufficiency as a cause, since there are studies in the literature that support the hypothesis that low placental weight can lead to fetal growth restriction. Salafia *et al.* [32] conducted a prospective study with the objective of determining the relationship between placental weight and birth weight variance and concluded that these are indeed correlated ($r = 0.59$). Hasegawa *et al.* [33] also endorsed that placental weight is lower in SGA than in the group of controls (462±113 vs 582±113, $p<0.001$). Nkwabong *et al.* [34] compared maternal medical records and placentas of term born (≥37 weeks) LBW (<2500g) or normal weight (3000-3500g) and noticed lower placental weight in LBW group [(468.3±87.9 (280-750) vs 655.6±133.5 (370-920), $p<0.0001$]. Therefore, it can be concluded that a

reduced placental weight, a signal of placental insufficiency, leads to fetal growth restriction, which in turn increases the incidence of hypospadias.

Besides, the identification of preeclampsia as a risk factor for hypospadias also supports the theory that placental insufficiency leads to FGR and hypospadias. The mechanism behind early preeclampsia and fetal growth restriction is, in both, placental dysfunction, likely caused by compromising utero-placental perfusion, and failed trophoblastic invasion of spiral arteries [35].

A strong point of our research is the absence of a restriction of publication date and the search in three databases, to avoid loss of important information. Another strength is the evaluation of the quality of the articles, using NIH Quality Assessment Tool, and most of the studies have low risk of bias. The methods used, emphasizing the construction of Table 1, that compiles the most relevant characteristics of each article, allows an easier comparison between articles and visualization of all the results and conclusions. In addition, since we excluded all studies in which the cases had anomalies potentially responsible for fetal growth restriction, most of the articles we included in this systematic review corroborate the placental cause as the most likely.

On the other hand, a limitation of our systematic review is the fact that most of the studies were conducted several years ago and, for this reason, there is little up-to-date information. Another important limitation is the difference in methodology and growth restriction criteria used in the various articles. It is important to establish criteria for fetal growth restriction to clearly distinguish preterm newborns from SGA and to avoid biases. Indeed, some of the articles included [26,27,28] do not evaluate the birth weight according to the gestational age, so it is not possible to determine if low birth weight is a result of FGR or preterm delivery in these cases, which could result in an over or under estimation of our conclusions. Due to the difficulty of defining FGR and SGA and to avoid differences in criteria, an international definition was developed, by expert consensus, through the Delphi procedure with the objective of standardizing and allowing comparison between studies [36].

In this way, we suggest that further studies be conducted in the context of genitourinary anomalies, focusing on populations with previously identified risk factors, with well-defined methodologies, guided by a universal definition of FGR. Above all, we recommend the anatomopathological study of placentas to better understand their role in the etiology of hypospadias.

Conclusion

Our review confirms an association between fetal growth restriction caused by placental insufficiency and hypospadias.

Declaration of Interest

None.

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Table 1: Characteristics of cohort, cross-sectional and case-control studies.

Author, year, country	Type of study	Population	Results	Conclusions
Boisen, K., 2005, Finland [13]	Prospective study	- N = 1072 - Cases = 39 - Controls = 852	- Mean weight for gestational age was significantly smaller [-5.00% (11.3) vs. -0.59% (12.4), p= 0.030] and placental weight was lower [567 g (108) vs. 658 g (142), p=0.023], compared with boys with no urogenital malformations. - Birth weight (p=0.027) and birth length (p=0.030) were smaller than in healthy boys. - At 3 months, was founded significantly higher levels of FSH (1.48 vs 1.15, p= 0.007) and higher FSH to inhibin B ratios (0.34 vs 0.29, p= 0.046) among boys with hypospadias, compared with healthy boys.	Hypospadias was associated with fetal growth impairment, and with elevated serum FSH levels at 3 months.
Chen, Y., 2016, China [22]	Retrospective study	- N = 27 407 - Cases = 167 - Controls = 15 613	- In 12 407 subjects (84.8%) without PMPC, the prevalence of hypospadias was 9 per 1000 boys. - Among 2.230 (15.2%) subjects who had PMPC, the prevalence was 22 per 1000 boys. - Hypospadias cases had higher incidence of SGA, compared with the controls (OR= 2.7, 95% CI: 1.8-3.4). - Hypospadias cases had higher risks of placental lesions.	Association between placental pathology resulting from placental insufficiency and hypospadias. Hypospadias was associated with SGA infants.
Dave, S., 2018, Canada [24]	Retrospective study	- N = 709 968 - Cases = 2722	- Hypospadias cases had a high incidence of boys SGA (OR= 1.8, 95% CI: 1.03-3.1).	Environmental exposures and genetic predisposition may be risk factors for hypospadias, which can confound known maternal and fetal risk factors for this anomaly.
Fujimoto, T., 2007, Japan [16]	Retrospective study	- N = 140 - Cases = 16 - Controls = 62	- Birth weight (824±160 vs 1255±145, p<0.01), birth weight SD score (-2.13±0.51 vs -0.33±0.51, p<0.01), birth length SD score (-1.45±0.64 vs -0.13±1.24, p<0.01), and head circumference SD score (-1.44±0.80 vs -0.12±1.11, p<0.01) at birth were lower in the patients with hypospadias compared with the controls. - Placenta to fetal weight ratio (0.323±0.07 vs 0.229±0.03, p<0.01) and placental weight to fetal age ratio (14.10±1.84 vs 8.53±2.06, p<0.01) were significantly higher in patients with hypospadias compared with the controls. - Histopathologic study of the placenta revealed infarction, calcification, and degenerative changes in the patients with hypospadias.	Increased incidence of isolated hypospadias among extremely LBW infants (<1500 g). Placental disorders including infarction, calcification, and degenerative changes are associated with SGA infants. Placental dysfunction in early gestation might play a significant role in the development of hypospadias and/or intrauterine growth retardation resulting in SGA.
Hashimoto, Y., 2015, Japan [19]	Retrospective study	- Cases = 16	- 9 babies were preterm and met the criterion for FGR. - 10 babies were LBW infants (<2500 g). - 2 placentas were inappropriately light for gestational age. - Infarct lesions were detected in 5 placentas. - 2 babies had single umbilical arteries.	Infants with FGR are more likely to have severe hypospadias, which is mostly caused by placental malfunction. Genital morphogenesis may be impacted by placental insufficiency caused by severe placental infarction or abnormal umbilical cord.

Author, year, country	Type of study	Population	Results	Conclusions
Hsieh, M. H., 2010, USA [29]	Retrospective study	- Cases = 54 - Controls = 34	- There is no difference in birth weight between males who have hypospadias and those without the condition (1541g vs 1875g, p=0.059).	The mean birth weight of males with hypospadias was not different from the mean birth weight of males without hypospadias.
Kovalenko, A. A., 2019, Sweden [26]	Retrospective study	- N = 25475 - Cases = 148 - Controls = 25 327	- The mean birth weight was lower in the group with hypospadias (3291g vs 3421g, p< 0.01). - Preeclampsia increased the risk for hypospadias (OR = 1.65; 95% CI 1.03–2.66).	Hypospadias was associated with LBW and preeclampsia.
Moretti, M., 1986, Italy [27]	Retrospective study	- N = 103 484 - Cases = 214	- 4.1 of 1000 newborn males had hypospadias. - IUGR was significantly associated (p<0.001) with hypospadias.	IUGR was more evident in the group with hypospadias.
Nissen, K. B., 2014, Denmark [21]	Retrospective study	- N = 131 778 - Cases = 196 isolated hypospadias - Controls = 67 587	- Isolated hypospadias were more likely to be a mild form. - Newborns with VLBW (<1500g) have a 3 times higher prevalence of hypospadias than do infants with normal birth weights [98.4 (95% CI 49.9–193.0) vs. 32.6 (95% CI 28.5–37.1)].	Low birth weight was inversely related to a high prevalence of hypospadias with greater than a three-fold higher risk for VLBW infants.
Pakniyat, A., 2016, Iran [28]	Cross-sectional study	- N = 1001 - Cases = 18 - Controls = 983	- More male newborns with hypospadias had birth weight <2500g, comparing to male newborns without hypospadias (7 vs 125, p=0.001).	Occurrence of hypospadias is associated with LBW.
Toufaily, M. H., 2017, USA [23]	Retrospective study	- N = 289 365 - Cases = 316	- Association with SGA infantes and hypospadias (frequency in sample=42 vs expected frequency if no association with centile group=26, p=0.0004) - The presence of IUGR or SGA birth weight was associated with more severe hypospadias (r =0.90; p = 0.10). - High frequency of maternal vascular malperfusion, inflammatory lesions, fetal vascular malperfusion, and anatomical abnormalities on boys with hypospadias.	IUGR and placental pathologies were associated with hypospadias.
Pierik, F. H., 2004, The Netherlands [25]	Case-control study	- N = 8698 - Cases = 56 - Controls = 313	- Univariate analysis: hypospadias was associated with LBW (OR= 4.1 95% CI: 1.7–9.8), and with being SGA (OR= 5.5 95% CI: 1.8–17.1). - Multivariate analysis: hypospadias was associated with preterm birth (OR= 3.1 95% CI: 1.5–6.6), and with being SGA (OR= 7.3 95% CI: 1.7–31.4).	LBW and SGA were associated with a higher risk of hypospadias.

LBW- Low birth weight; SGA- Small for gestational age; AGA- Appropriate for gestational age; FSH- Follicle-Stimulating Hormone; PMPC- Placenta-mediated pregnancy complications; FGR- Fetal growth restriction; NICUs – Neonatal Intensive Care Units; LGA- Large for gestational age; IUGR- Intrauterine growth restriction; VLBW- Very low birth weight.

Table 2: Risk of bias using the NIH Study Quality Assessment Tool. Risk of bias was graded as Good "ii" (11 to 14 ✓), Fair "i" (5 to 10 ✓), and Poor "0" (0 to 4 ✓).

Study	Was the research question or objective in this paper clearly stated?	Was the study population clearly specified and defined?	Was the participation rate of eligible persons at least 50%?	Were all the subjects selected or recruited from the same or similar populations?	Was a sample size justification, power description, or variance and effect estimates provided?	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	For exposures that can vary in amount or level, did the study examine different levels of the exposure?	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the exposure(s) assessed more than once over time?	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the outcome assessors blinded to the exposure status of participants?	Was loss to follow-up after baseline 20% or less?	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Summary Quality
Boisen, K., 2005, Finland [13]	✓	✓	✓	✓	X	✓	✓	NA	✓	✓	✓	X	X	✓	i
Chen, Y., 2016, China [22]	✓	✓	X	✓	X	X	✓	NA	✓	✓	✓	✓	NR	✓	i
Dave, S., 2018, Canada [24]	✓	✓	X	✓	X	X	✓	NA	NR	NR	NR	X	NR	✓	i
Fujimoto, T., 2007, Japan [16]	✓	✓	X	✓	X	✓	✓	NA	✓	X	NR	X	NR	X	i
Hashimoto, Y., 2015, Japan [19]	✓	✓	✓	✓	X	X	✓	NA	✓	NR	✓	X	NR	X	i
Hsieh, M. H., 2010, USA [29]	✓	✓	✓	✓	X	X	✓	NA	✓	✓	✓	X	NR	X	i
Kovalenko, A. A., 2019, Sweden [26]	✓	✓	X	✓	X	X	✓	NA	NR	NR	NR	X	NR	✓	i
Moretti, M., 1986, Italy [27]	X	✓	X	✓	X	X	✓	NA	NR	NR	NR	X	NR	X	0
Nissen, K. B., 2014, Denmark [21]	✓	✓	X	✓	X	X	✓	NA	✓	X	✓	X	NR	X	i
Pakniyat, A., 2016, Iran [28]	✓	✓	✓	✓	X	X	X	NA	✓	X	✓	X	NR	X	i
Toufaily, M. H., 2017, US [23]	✓	✓	NR	✓	X	X	✓	NA	✓	✓	✓	X	NR	NR	i

Table 3: Risk of bias using the NIH Study Quality Assessment Tool. Risk of bias was graded as Good "ii" (10 to 12 ✓), Fair "i" (4 to 9 ✓), and Poor "0" (0 to 3 ✓).

Study	Was the research question or objective in this paper clearly stated and appropriate?	Was the study population clearly specified and defined?	Did the authors include a sample size justification?	Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Were the cases clearly defined and differentiated from controls?	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	Was there use of concurrent controls?	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Were the assessors of exposure/risk blinded to the case or control status of participants?	Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Summary Quality
Pierik, F. H., 2004, The Netherlands [25]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	NR	✓	ii

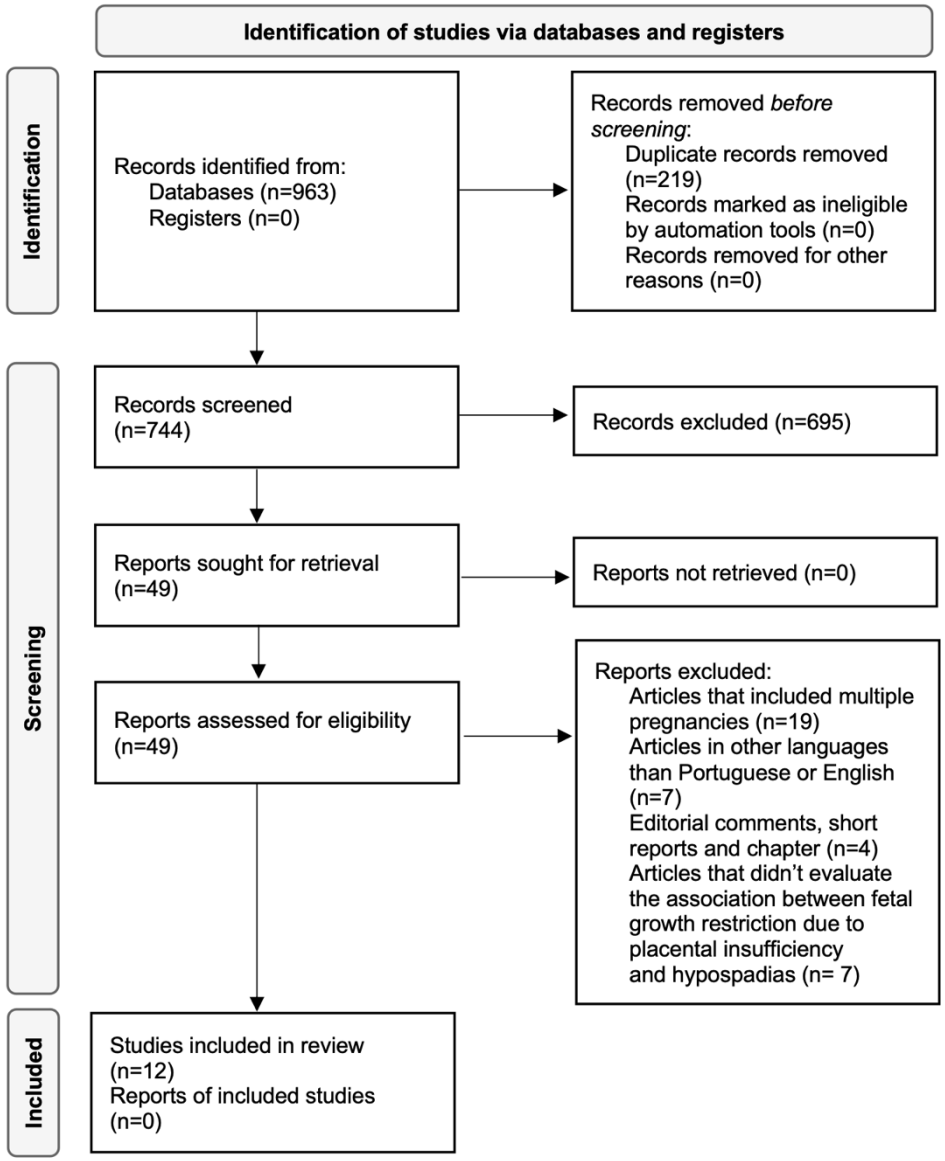

Figure 1: PRISMA flow diagram for included studies.

Attachments

I. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 6: "Systematic review: Is there a connection between the fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies?"
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 24
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 8, 3rd to 5th paragraph: "Among all the risk factors that have been implicated in hypospadias, being small for gestational age is thought to be one of the most important, and is a topic explored by several studies."
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 8, 6th paragraph: "The aim of our study is to understand the association between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies."
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8, 8th paragraph: "We included observational and human studies that evaluated the association between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies. Animal studies, case reports or systematic reviews, and studies in which the cause of fetal growth restriction was genetics were excluded. Only studies in English and Portuguese were included. There was no publication date restriction."
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8, 7th paragraph: "The literature search was performed in February 2022 in three databases - PubMed, Scopus, and Web of Science, using the query: (Hypospadias) AND (Small for gestational age OR Intrauterine growth retardation OR Intrauterine growth restriction OR Fetal growth restriction OR Fetal growth retardation OR Low birth weight)."
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 8, 7th paragraph: "The literature search was performed in February 2022 in three databases - PubMed, Scopus, and Web of Science, using the query: (Hypospadias) AND (Small for gestational age OR Intrauterine growth retardation OR Intrauterine growth restriction OR Fetal growth restriction OR Fetal growth retardation OR Low birth weight)."
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8, 10th paragraph: "After the removal of the duplicates, the selection of the articles obtained from databases were done independently by two authors. This step was based on the titles and abstracts analyses. Any disagreement in the inclusion of the studies was resolved by consensus. Afterwards, one of the reviewers had read the full-text articles assessed for eligibility."
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 9, 1st paragraph: "The data extraction from the included studies was performed manually by one of the authors. The data extracted (authors, publication year, the country where the study was performed, study design, objective, sample, control group, results, and conclusions) was introduced into a table."
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9, 1st paragraph: "The data extraction from the included studies was performed manually by one of the authors. The data extracted (authors, publication year, the country where the study was performed, study design, objective, sample, control group, results, and conclusions) was introduced into a table."
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9, 1st paragraph: "The data extraction from the included studies was performed manually by one of the authors. The data extracted (authors, publication year, the country where the study was performed, study design, objective, sample, control group, results, and conclusions) was introduced into a table."

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9, 2nd paragraph: "The risk of bias was measured using the NIH Study Quality Assessment Tool, NIH quality assessment tool for observational cohort and cross-sectional studies and NIH quality assessment tool for case-control studies."
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable, as this systematic review does not include a meta-analysis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable, as this systematic review does not include a meta-analysis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable, as this systematic review does not include a meta-analysis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable, as this systematic review does not include a meta-analysis
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable, as this systematic review does not include a meta-analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable, as this systematic review does not include a meta-analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable, as this systematic review does not include a meta-analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable, as this systematic review does not include a meta-analysis
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable, as this systematic review does not include a meta-analysis
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, 3rd paragraph: "The result of the database searching was a total of 963 articles, 207 on PubMed, 551 on Scopus, and 205 on Web of Science. After removing the 219 duplicates, the selection started with the title and abstract analysis, which resulted in the inclusion of 49 articles and the exclusion of 695 which did not meet the eligibility criteria. Thereafter, a full text analysis was conducted, and leaving a total of 12 articles that were included in this systematic review. The entire search and selection strategy were described in the Figure 1."
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9, 3rd paragraph: "After removing the 219 duplicates, the selection started with the title and abstract analysis, which resulted in the inclusion of 49 articles and the exclusion of 695 which did not meet the eligibility criteria. Thereafter, a full text analysis was conducted, and leaving a total of 12 articles that were included in this systematic review."
Study characteristics	17	Cite each included study and present its characteristics.	Page 9, 3rd paragraph: "The relevant data of the studies included are registered in Table 1."
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9, 5th paragraph: "The assessment of the risk of bias for cohort and cross-sectional studies is present in Table 2, and for case-control study in Table 3."
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable, as this systematic review does not include a meta-analysis

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable, as this systematic review does not include a meta-analysis
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable, as this systematic review does not include a meta-analysis
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable, as this systematic review does not include a meta-analysis
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable, as this systematic review does not include a meta-analysis
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable, as this systematic review does not include a meta-analysis
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable, as this systematic review does not include a meta-analysis
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10, 5th and 6th paragraphs, Page 11, 1st paragraph: "So, as already concluded placental insufficiency are associated with SGA infants, who, have a higher prevalence of hypospadias."
	23b	Discuss any limitations of the evidence included in the review.	Page 11, 3rd paragraph: "Another important limitation is the difference in methodology and growth restriction criteria used in the various articles."
	23c	Discuss any limitations of the review processes used.	Page 11, 3rd paragraph: "On the other hand, a limitation of our systematic review is the fact that most of the studies were conducted several years ago and, for this reason, there is little up-to-date information."
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11, 4th paragraph: "In this way, we suggest that further studies be conducted in the context of genitourinary anomalies, focusing on populations with previously identified risk factors, with well-defined methodologies, guided by a universal definition of FGR."
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not applicable
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not applicable
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 11, 7th paragraph: "This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors."
Competing interests	26	Declare any competing interests of review authors.	Page 11, 6th paragraph: "None."
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

II. PRISMA 2020 Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes, “We performed a systematic review searching on PubMed, Web of Science and Scopus databases.”
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes, “Our aim is to comprehend the correlation between fetal growth restriction (FGR) due to placental insufficiency and hypospadias in single pregnancies.”
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes, “Articles evaluating the association between fetal growth restriction due to placental insufficiency and hypospadias in single pregnancies were included.”
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes, “We performed a systematic review searching on PubMed, Web of Science and Scopus databases.”
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes, “The risk of bias was measured using the NIH Study Quality Assessment Tool.”
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes, “A total of 12 studies were included, and their relevant data were extracted and qualitatively analyzed.”
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes, “Seven articles reported that fetal growth restriction and small for gestational age are important risk factors for the development of hypospadias. Four studies concluded that low birth weight is associated with the higher prevalence of hypospadias. Only one study found no significant differences between the birth weight of boys with and without hypospadias.”
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes, “Seven articles reported that fetal growth restriction and small for gestational age are important risk factors for the development of hypospadias. Four studies concluded that low birth weight is associated with the higher prevalence of hypospadias. Only one study found no significant differences between the birth weight of boys with and without hypospadias. In four studies anatomopathological evaluations of the placenta was performed, and in all signs of placenta dysfunction was more frequent in infants with hypospadias. Five studies evaluated the weight of placenta, and concluded that weight of placenta of boys with hypospadias was lower than weight of placenta of healthy boys. Two studies found preeclampsia as a risk factor for hypospadias.”
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes, “The major limitations of our review are the differences in methodology of the studies included, most of them conducted several years ago.”
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes, “Our results highlight fetal growth restriction as a potential cause of increased prevalence of hypospadias.”
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

JOURNAL OF PEDIATRIC UROLOGY

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AUTHOR INFORMATION PACK

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To advance and improve the education in **Pediatric Urology** and the diffusion of knowledge of new and improved methods of teaching and practising pediatric urology in all its branches.

Scope:

The *Journal of Pediatric Urology* publishes submitted research and clinical articles relating to Pediatric Urology which have been accepted after adequate peer review.

It publishes regular articles that have been submitted after invitation, that cover the curriculum of Pediatric Urology, and enable trainee surgeons to attain theoretical competence of the sub-specialty.

It publishes regular reviews of pediatric urological articles appearing in other journals.

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Only guidelines, standardization, consensus papers, reviews, short communications and correspondence articles will be published in full in the print version of the Journal. For all other articles the print version of the Journal will include only structured summaries, with the full length version of the article appearing online. Therefore, an extended structured summary is required for all original research articles submitted to the Journal from now on as part of the full length article. Guidelines for the structured summaries are below and more details on the structure can be found in the section, Essential title page information

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* Original Research - 3,000 words, extended summary 400 words and a figure/table, 30 references, 4 figures or tables
Review Article - 4,000 words, summary 300 words, 40 references, 4 figures or tables
Survey Article - 3,000 words, extended summary 400 words and a figure/table, 30 references, 4 figures or tables
Requirements for Survey Articles can be found Here
Short Communication 'How do I do it' - 500 words, summary 100 words, 5 references, 4 figures or tables
Educational Article - 3,000 words, summary 300 words, 30 references, 4 figures or tables
Correspondence and Commentaries - 500 words, 5 references
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New instructions for authors specific to survey studies submitted to JPU
Nelson, Caleb P. Journal of Pediatric Urology, Volume 16, Issue 4, 416-4170

Application of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to publications on endoscopic treatment for vesicoureteral reflux
Farrugia, M.K. et al. Journal of Pediatric Urology, Volume 13, Issue 3, 320-325

Application of the STROBE statement to the hypospadias literature: Report of the international pediatric urology task force on hypospadias
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