SYSTEMATIC REVIEW

Population variation in Y-chromosome microdeletion and its role in the evaluation of male infertility management: a systematic review [version 1; peer review: 1 approved]

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Abstract

Background: Infertility has been a significantly growing problem worldwide, affecting approximately 10-15% of couples within reproductive age. Among the many causes of male infertility, Y-chromosome microdeletion is considered one of the most frequent genetic causes. Thus, this systematic review was constructed to determine the prevalence of Y-chromosome microdeletion and the population variations in the different types of Y-chromosome microdeletions.

Methods: We searched the PubMed, Scielo, and Science Direct databases to obtain articles that addressed the frequency of Y-chromosome microdeletion and male infertility. We identified 14 articles that originated from China, India, Iran, Brazil, Indonesia, North America, South Korea, and Slovakia, and the vital information collected included the year of publication, authors, number of patients with different types of Y-chromosome microdeletions, and the proportion of microdeletion in the major affected sub-regions of the Y-chromosome.

Results: In this review, we attempted to highlight the variation in the frequency of Y-chromosome microdeletion in different geographical populations. The highest and lowest frequencies of Y-chromosome microdeletion were found in Indonesian (23.94%) and Slovakian (3.5%) populations, respectively.

Conclusion: In conclusion, Y-chromosome microdeletion was undeniably found to be one of the leading genetic causes of male infertility. Azoospermic factor c (AZFc) microdeletion was the most frequent type of Y-chromosome microdeletion, typically presenting in patients with various clinical manifestations that ranged from oligozoospermia to azoospermia and exhibiting the highest chance for sperm retrieval. This review will undoubtedly help clinicians in providing a more accurate consultation to their patients and determining the success rates of assisted reproductive technology.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
microdeletion, Y chromosome, azoospermia, oligozoospermia, male infertility

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Introduction

Infertility has been a major growing problem worldwide, affecting approximately 10-15% of couples within reproductive age; approximately 30-50% of these cases are attributable to male factors.[1] Among the many causes of male infertility, Y-chromosome microdeletion is considered one of the most frequent genetic causes.[2] The Y-chromosome, consisting of a short arm (Yp) and a long arm (Yq), has been long known as one of the sex-determining chromosomes. Y-chromosome microdeletions are interstitial deletions that occur in the azoospermic factor (AZF) region in the Yq. Microdeletions affect testis development, consequently leading to the manifestation of azoospermia or oligozoospermia in the affected patients.[3,4] Clinically, there are three important non-overlapping regions in the AZF gene, including the azoospermia factor a (AZFa), azoospermia factor b (AZFb), and azoospermia factor c (AZFc), and they correspond to five microdeletion patterns, AZFa, AZFb, AZFc, AZFbc, and AZFabc.[4]

Y-chromosome microdeletion testing is considered an essential part of infertility evaluation of severely oligozoospermic or azoospermic men. This is especially true for couples who are considering using assisted reproductive technology [(ART - in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)].[5,6] However, Y-chromosome microdeletion analysis is not a common practice in various infertility centers despite its acknowledged benefits. This is attributable to the cost imposed on the patients and the limited coverage of this examination by most existing health insurance companies.[7] One other possible reason for this variation in Y-chromosome microdeletion testing is the differing frequencies of Y-chromosome microdeletions in different geographical areas. Smaller studies from various countries have shown that the frequency of Y-chromosome microdeletion ranges from 1-14%.[8] This indicates that the cost-effectiveness and necessity of this particular test are deteriorated in regions where Y-chromosome microdeletions are relatively less frequent.

Therefore, this review was conducted to gather the most recent clinical evidences that document the prevalence of and population variation in Y-chromosome microdeletions; we attempted to highlight the variation in the prevalence of Y-chromosome microdeletion in different geographical populations.

Methods

Evidence acquisition

Search strategy and selection criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.[9] A comprehensive literature search of three different databases (PubMed, Scielo, and Science Directs) was performed using the following keywords: "Y-Chromosome" OR "Y-chromosome" AND "microdeletion," AND "male infertility". The keywords were the same for all databases. The search was limited to studies published within the last 10 years. The articles included in this review were selected based on the following predetermined inclusion criteria: (1) articles written in English, (2) articles that addressed the frequency of Y-chromosome microdeletion and male infertility, and (3) original studies with readily available full-text articles. On the other hand, the exclusion criteria included: (1) other type of articles including letters to the editor, reviews, and editorials; (2) articles that included patients with chromosomal abnormalities; and (3) articles that included patients who had undergone radiotherapy and chemotherapy. Duplicated manuscripts obtained from more than one database were counted as only one article.

Initial screening from titles and abstracts of the articles was done independently by two investigators (PB and IAD). The full texts of potentially relevant articles, or articles where no decision could be made from the abstract, were then reviewed. If there was any disagreement, the decision was made through discussion with other investigators (NR and WD). This search strategy yielded 141 results from the three above-mentioned databases, and three duplicated articles were automatically omitted. The abstracts of the remaining articles were screened to select the articles that were relevant to this review. As a result, 112 articles were excluded, leaving 26 articles for further investigation and evaluation of the full-text article. Finally, 12 studies were excluded, and 14 studies were found to be eligible for this review. The search strategy performed in this review is summarized in Figure 1.

Quality assessment

The quality of each study was assessed using a tool developed by Hoy *et al.*[10] to assess the risk of bias in prevalence studies. 10 domains were assessed based on internal and external validity of the studies: representativeness of the data, sampling methods, sample selection, likelihood of non-response bias, data collection, case definitions used, reliability and validity of the instruments, similarity of mode of data collection, length of prevalence period, and reliability of the calculations. Each domain was given a score of one (yes) or zero (no). Studies were classified as having low risk, moderate risk and high risk of bias if the overall score were >8, 6-8, and ≤5 respectively.

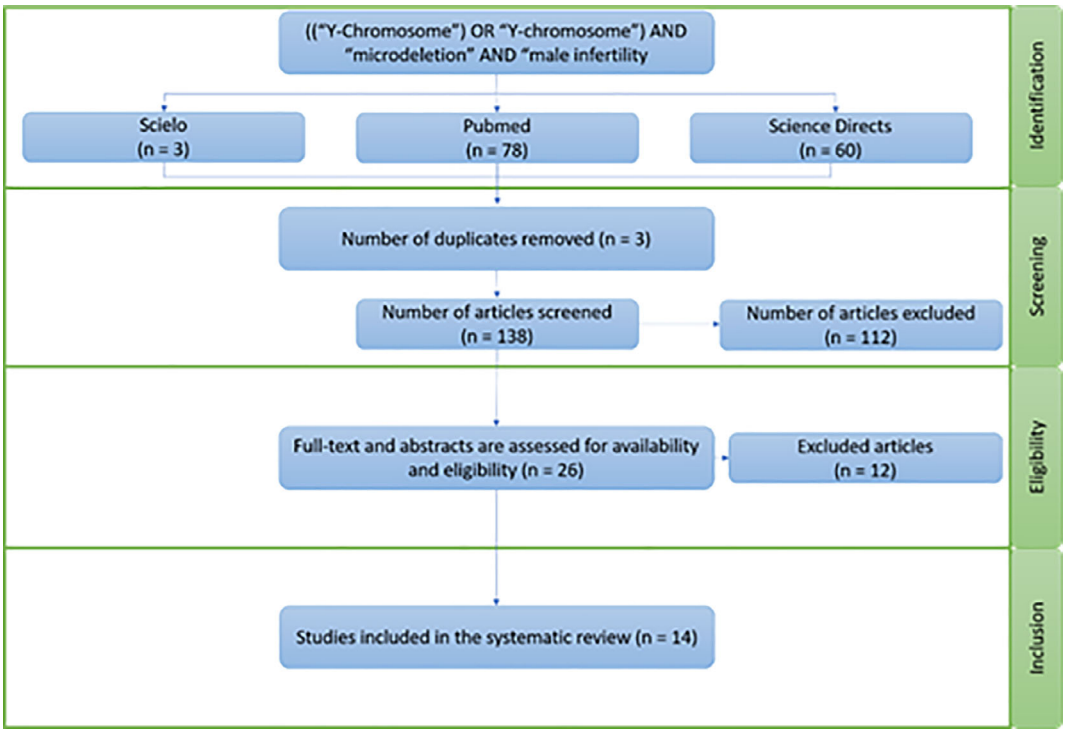

Figure 1. Study flow diagram.

Data extraction

The data from the selected articles were then extracted independently by two authors (PB, IAS) using a standardized data extraction form that included the year of publication, authors, the number of patients with different types of Y-chromosome microdeletions, and the proportion of microdeletion in the major affected sub-regions of the Y-chromosome. Any discrepancy on the data extracted were solved by discussion and reference to the original article to meet the consensus.

Results

The search strategy yielded 138 manuscripts from the three databases after omitting the duplicated articles, as previously mentioned. After a careful and thorough review of the titles, abstracts, and the main manuscripts, 14 articles were found to be eligible for this review; see flowchart.[26] From these 14 articles, five manuscripts originated from China, two each from India and Iran, and one each from Brazil, Indonesia, North America, South Korea, and Slovakia. All the important data of these 14 articles were concisely summarized, as shown in Table 1. From the risk of bias assessment, no study was found to have higher risk of bias. 8 of 14 studies included have an intermediate risk of bias whereas the rest have a low risk of bias. Quality of assessment results are also summarized in Table 1.

Variation in the frequency of Y-chromosome microdeletion in different geographical populations was observed. The highest and lowest frequencies of Y-chromosome microdeletion were found in Indonesian (23.94%) and Slovakian (3.5%) populations, respectively. AZFc microdeletions were identified as the most common Y-chromosome microdeletions, exhibiting the highest chance for sperm retrieval. The rates of Y-chromosome microdeletions, along with the percentages of the affected sub-regions of the Y-chromosome, in each country were listed and summarized in this review, as shown in Figure 2.

Discussion

Epidemiological aspects of Y-chromosome microdeletion

Approximately 10-15% of couples within reproductive age worldwide face infertility problems. Male infertility contributes to approximately 30-50% of these cases.[1] Y-chromosomal microdeletion is ranked second, after Klinefelter Syndrome, in the most common genetic causes of male infertility.[6] Y-chromosome microdeletion affects testicular development greatly, phenotypically manifesting as azoospermia or oligozoospermia.[4] The frequency of Y-chromosome microdeletion found in this review ranged from 1.7% to 23.9%. The high variability of Y-chromosome microdeletion

Table 1. Proportions of the infertile patients diagnosed with Y-chromosome microdeletions, along with the affected sub-regions of the Y-chromosome. AZFa, azoospermia factor a; AZFb, azoospermia factor b; AZFc, azoospermia factor c.

Author (Year)	Country	Patients with Y-chromosome microdeletion (N)	AZFa	AZFb	AZFc	Others	Risk of bias assessment
Liu *et al.* (2019)[9]	China	164 out of 1274 (12.87%) patients with azoospermia or oligozoospermia,	4/164 (2.44%)	11/164 (6.71%)	102/164 (62.20%)	AZFbc [41/164 (25%)] AZFabc [6/164 (3.6%)]	9 (low risk)
de Sousa Filho *et al.* (2018)[10]	Brazil	2 out of 51 (3.9%) infertile men with varicocele and either oligozoospermia or azoospermia	-	-	1/2 (50%)	AZFbc [1/2 (50%)]	7 (intermediate risk)
Birowo *et al.* (2017)[11]	Indonesia	17 out of 71 (23.94%) patients with azoospermia or severe oligozoospermia	11/17 (64.7%)	1/17 (5.8%)	1/17 (5.8%)	AZFab [2/17 (11.6%)] DBY gene exon 2 deletion [2/17 (11.6%)]	8 (intermediate risk)
Zhu *et al.* (2017)[12]	China	150 out of 1801 (8.3%) patients with spermatogenic failure were diagnosed with Y chromosome microdeletions	7/150 (4.67%)	6/150 (4%)	110/150 (73%)	AZFbc [17/150 (11.3%)] AZFabc [10/150 (6.7%)]	10 (low risk)
Liu XG *et al.* (2016)[13]	China	28 out of 166 (16.8%) patients with azoospermia or oligospermia	6/28 (21.40%)	3/28 (10.70%)	15/28 (53.60%)	AZFabc [4/28 (14.30%)]	8 (intermediate risk)
Dai R L *et al.* (2015)[14]	China	58 out of 1200 (4.8%) infertile patients, including 36 azoospermic and 22 oligozoospermic patients	3/58 (5.17%)	3/58 (5.17%)	41/58 (70.68%)	AZFbc [11/58 (18.96%)]	10 (low risk)
Sen *et al.* (2013)[15]	India	215 out of 3647 (5.9%) infertile patients with azoospermia and severe oligozoospermia	25/215 (11.6%)	22/215 (10.1%)	100/215 (46.6%)	AZFab [12/215 (5.8%)] AZFbc [42/215 (19.6%)] AZFac [7/215 (3.2%)] AZFabc [7/215 (3.2%)]	8 (intermediate risk)
Saliminejad *et al.* (2012)[16]	Iran	2 out of 115 (1.7%) infertile patients with azoospermia	-	-	1/2 (50%)	AZFbc [1/2 (50%)]	8 (intermediate risk)
Totonchi *et al.* (2012)[17]	Iran	185 out of 3654 (5.06%) infertile patients	4/185 (2.16%)	8/185 (4.32%)	95/185 (51.35%)	AZFabc (Yq) [29/185 (15.67%)] AZFac [1/185(0.54%)] AZFbc [29/185 (15.67%)] AZF Partial a [1/185 (0.54%)] AZF Partial b [3/185 (1.62%)] AZF Partial c [3/185 (1.62%)] AZFb+partial c [7/185 (3.78%)] AZFc+partial b [5/185 (2.70%)]	9 (low risk)

Table 1. *Continued*

Author (Year)	Country	Patients with Y-chromosome microdeletion (N)	AZFa	AZFb	AZFc	Others	Risk of bias assessment
Kim *et al.* (2012)[18]	Korea	101 out of 1306 (7.7%) infertile patients	5/101 (4.9%)	8/101 (7.9%)	55/101 (54.4%)	AZFbc [24/101 (23.8%)] AZF abc [9/101 (8.9%)]	9 (low risk)
Fu *et al.* (2012)[19]	China	144 out of 1333 (10.8%) infertile patients with azoospermia or severe oligozoospermia	13/144 (9.03%)	15/144 (10.42%)	78/144 (54.17%)	AZFab [3/144 (2.08%)] AZFac [3/144 (2.08%)] AZFbc [27/144 (18.75%)] AZFabc [5/144(3.47%)]	9 (low risk)
Behulova *et al.* (2011)[20]	Slovakia	8 out of 226 (3.53%) infertile patients	2/8 (25%)	0/8 (0%)	4/8 (50%)	AZFbc [1/8 (12.5%)] AZFabc [1/8 (12.5%)]	7 (intermediate risk)
Pandey *et al.* (2010)[21]	India	2 out of 64 (3.1%) patients with azoospermia and severe oligozoospermia	-	-	2/2 (100%)	-	7 (intermediate risk)
Stahl *et al.* (2010)[4]	North America	149 out of 1591 (9.4%) patients with azoospermia and oligozoospermia	4/149 (2.6%)	17/149 (11.4%)	78/149 (52.3%)	AZFbc [32/149 (21.4%)] AZFabc [18/149 (12.1%)]	8 (intermediate risk)

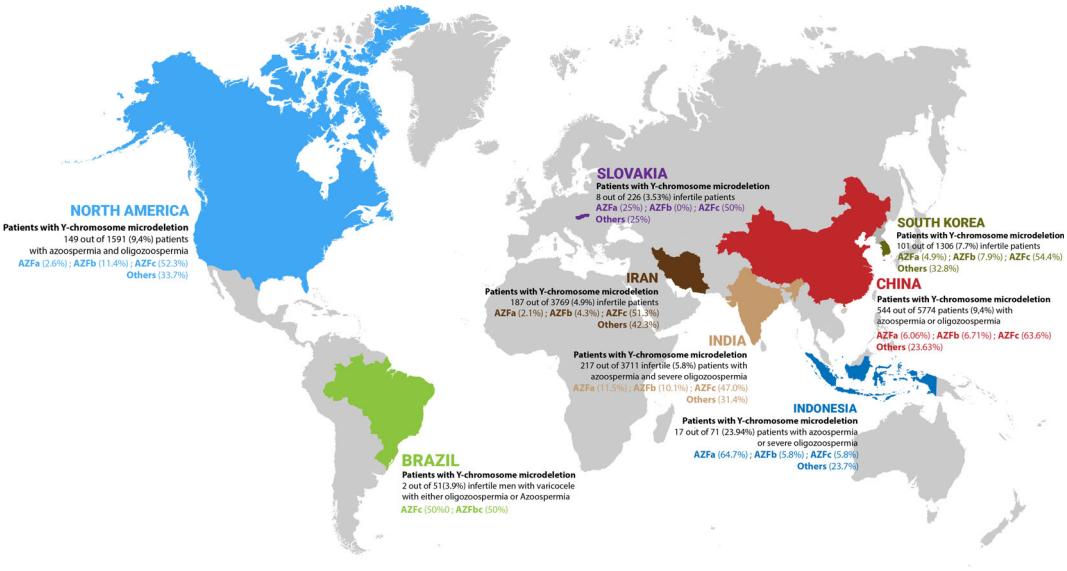

Figure 2. The rates of Y-chromosome microdeletion, along with the percentages of the affected sub-regions of the Y-chromosome, in each country (*The World Map Image is available from Wikipedia*, 31 August 2011, *https://en.wikipedia.org/wiki/File:Simple_world_map.svg*). The figure is under the terms of the Creative Commons Zero "No rights reserved" data waiver. AZFa, azoospermia factor a; AZFb, azoospermia factor b; AZFc, azoospermia factor c.

among the different studies in this review mainly depended on the number of samples recruited in each study and the manner in which the samples were recruited. One study by Birowo P *et al.* in Indonesia reported the frequency of Y-chromosome microdeletion to be approximately 23.9% (17 out of 71 patients with non-obstructive azoospermia or severe oligozoospermia). Another study conducted by Saliminejad *et al.* in Iran showed that only 1.7% (2 out of 125) male infertility patients showed complete AZFc deletion. These two patients presented with non-obstructive azoospermia, while all other patients included in the oligozoospermia group in this particular study did not present with Y-chromosome microdeletions at all.[16] Discrepancy in the frequency of Y-chromosome microdeletion was also observed in another study conducted by Totonchi *et al.* in a different institution in Iran. According to the results of this study, approximately 5.06% (185 out of 3654) infertile patients, enrolled from 2005 to 2011, were diagnosed with Y-chromosome microdeletion and a majority of the patients (74.96%) showed azoospermia.[19] This discrepancy in Y-chromosome microdeletions was also observed among the studies conducted in different regions of China. For instance, Liu *et al.* conducted a retrospective study in southwestern China and found that 12.87% (185 out of 1274) infertile patients were diagnosed with Y-chromosome microdeletion.[11] Another comparably large study conducted by Dai *et al.* in northeastern China reported the frequency of Y-chromosome microdeletion to be 4.8% (58 out of 1200 patients). This clearly showed that variation in the frequency of Y-chromosome microdeletion was observed in not only different countries, but also different regions of a particular country.

Important affected sub-regions of the Y-chromosome

A 10-year cohort study conducted by Stahl *et al.* in North America showed that AZFc Y-chromosome microdeletions harbor the most common type of Y-chromosome microdeletions [78 out of 149 patients (52.3%)]. Patients diagnosed with this particular type of Y-chromosome microdeletion presented with various sperm concentration-related clinical manifestations ranging from oligozoospermia (3.8%) to severe oligozoospermia (32.1%) and azoospermia (64.2%). The other patients, who were mainly included in the azoospermia group [54 out of 55 patients (98.1%)], were diagnosed with other types of Y-chromosome microdeletions, including AZFa, AZFb, AZFbc, and complete Yq deletions.[4] This finding that AZFc Y-chromosome microdeletions are the most commonly diagnosed Y-chromosome microdeletions with incidence ranging from 46.6% to 100% was concurrent with the findings of other studies conducted in Brazil, China, India, Iran, and Korea.[11–13,22–24] However, one study conducted by Birowo *et al.* in Indonesia reported AZFa Y-chromosome microdeletions (64.7%), instead of AZFc Y-chromosome microdeletions, to be the most frequent type of deletion. The high prevalence of partial AZFa microdeletion (absent sY84, present sY86) could be attributed to the larger proportion of azoospermic patients recruited in this study (only 2 out of 17 patients presented with severe oligozoospermia). Additionally, it could be explained by the possibility of a single-nucleotide polymorphism (SNP), increasing the false positive results of AZFa microdeletions. This SNP, which is common in the Chinese ethnic group, includes a single-nucleotide conversion of T to G in the target sequence of the reverse sY84 primer (rs72609647). It can only be determined by sequencing the sY84 locus.[13,25]

Clinical implications of Y-chromosome microdeletions

Y-chromosome microdeletion is one of the leading genetic causes of male infertility, greatly affecting testicular development.[5] Birowo P *et al.* analyzed the testicular histology of two patients with partial AZFa deletion, one with AZFb deletion, and one with DBY gene exon 2 deletion. The testicular histology of the patient with AZFb deletion showed maturation arrest at the primary spermatocyte stage in all tubules, while that of the patient with DBY gene exon 2 deletion showed Sertoli cell only (SCO) syndrome. The testicular histology of the two patients with partial AZFa deletion indicated divergent spermatogenesis activity among the tubules. All four patients typically presented with azoospermia.[13] Y-chromosome microdeletion evaluation also provides a deeper insight into the possibility of success of utilizing ART.[4,11,24] In general, AZFc deletion typically presents with various sperm concentration-related clinical manifestations ranging from oligozoospermia to azoospermia. Stahl *et al.* successfully exhibited a sperm retrieval rate as high as 71.4% in azoospermic patients with AZFc deletion by microTESE. However, no successful sperm retrieval was observed in the AZFa, AZFb, AZFbc, and AZFabc (Yq) deletion groups. Additionally, Liu *et al.* demonstrated that almost half (45.1%) the patients with AZFc deletion developed oligozoospermia, consequently indicating that a high sperm retrieval rate in these patients can be achieved by self-ejaculation instead of invasive surgical procedures. Furthermore, in terms of hormonal levels, younger oligozoospermic patients (21-30 years) with AZFc deletion typically exhibited higher testosterone and estradiol and lower follicle-stimulating hormone and luteinizing hormone expression levels.[11] This information allowed us to make an important finding that patients diagnosed with AZFc deletion showed higher chances of sperm retrieval for IVF/ICSI.

Conclusion

In conclusion, Y-chromosome microdeletion was undeniably found to be one of the leading genetic causes of male infertility. Y-chromosome microdeletion screening, although costly, may be potentially useful in geographical regions where high frequency of Y-chromosome microdeletion is exhibited. In this systematic review, the highest and lowest frequencies of Y-chromosome microdeletion were found in Indonesia (23.94%), despite the possibility of false positive results due to the SNP, and Slovakia (3.5%), respectively. One of the limitations of this review was the discrepancy in the number of samples recruited in each of the included studies, possibly affecting the variation in the overall rates of Y-chromosome microdeletions. Nevertheless, almost all the studies included in this systematic review showed that AZFc microdeletion was the most frequent type of Y-chromosome microdeletion, typically presenting with various clinical manifestations that ranged from oligozoospermia to azoospermia and exhibiting the highest chance for sperm retrieval. This review will certainly help clinicians in providing a more accurate consultation to their patients and determining the success rates of ART.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Open Science Framework: PRISMA checklist and flow diagram for 'Population variation in Y-chromosome microdeletion and its role in the evaluation of male infertility management: A systematic review', https://doi.org/10.17605/OSF.IO/RVUW7.[26]

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The authors have clearly stated the rationale and the objectives of the study, i.e. to gather the most recent clinical evidence that document the prevalence of and population variation in Y-chromosome microdeletion; and the variation in different geographical populations. The authors adhered to the PRISMA reporting guidelines, the inclusion criteria, as well as the information sources, search strategies, data collection, quality assessment, and outcomes are also clearly outlined. The conclusion drawn was adequately supported by the data; also the limitations of this review. This systematic review will have a great impact on the practice of male infertility treatment.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.