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Infertility Worldwide: The Lack of Global Pediatric Andrologists and Prevention

*Zampieri Nicola, Bianchi Federica, Patanè Simone,
Vestri Elettra and Camoglio Francesco Saverio*

Abstract

Andrology is the medical specialty dealing with men's health and reproductive system, including the genital, hormonal, reproductive, sexual, as well as psychological aspects, from birth to adulthood. Regular andrological checkups are essential both to reveal possible problems and to receive thorough advice and information so as to ensure that sexual and reproductive functions are well preserved. Estimates report that about one in three males suffers from andrological diseases, their rates varying according to the age: 27–30% of pediatric male subjects have reproductive and/or sexual conditions. In adulthood, 40% of men are affected by andrological diseases, in particular infertility and sexual problems. We studied medical literature about infertility, its prevention, and its treatment; our outcomes were to evaluate the role of research to prevent infertility especially in pediatric and adolescent age. The analysis of the data shows that in absolute numbers, the conditions directly associated with infertility are less studied than the treatment with medically assisted procreation. This research is intended as a warning to the countries worldwide: all those involved in the pediatric treatment area should be stimulated to act toward this goal, and each country should bear the responsibility of promoting and financing andrological screening campaigns.

Keywords: infertility, varicocele, pediatric, adolescence, undescended testes, medical-assisted reproduction

1. Introduction

Andrology is the medical specialty dealing with men's health and reproductive system, this including the genital, hormonal, reproductive, sexual, as well as psychological aspects, from birth to adulthood. Regular andrological checkups are essential both to reveal possible problems and to receive thorough advice and information as to ensure that sexual and reproductive functions are well preserved.

Estimates report that about one in three males suffers from andrological diseases, their rates varying according to the age: 27–30% of pediatric male subjects have reproductive and/or sexual conditions, especially cryptorchidism, varicocele, hypogonadism, congenital anomalies of the genitourinary tract, and sexually transmitted diseases. In adulthood, 40% of men are affected by andrological diseases, in

particular infertility and sexual problems. The main surgically correctable diseases to prevent hypofertility are varicocele (30%) and undescended testes (<5%) [1–3].

The origin of many of the andrological conditions appearing during adulthood is to be traced before the age of 18 and sometimes even during gestation. The male gonad is extremely sensitive to external events even during gestation and soon after childbirth up until puberty. The andrological evaluation of pediatric patients is therefore extremely important for the early diagnosis of genital anomalies such as penile alterations or abnormal positions of the testis; early evaluation is helpful also to search for risk factors in terms of male general and sexual health.

Andrology greatly trusts primary prevention to reduce the incidence of andrological diseases and conditions. Clinical studies and primary prevention interventions in andrology should be focused on the most vulnerable crucial phases of male gonad development that can be affected by a variety of external agents.

The preservation of the genital and sexual health of young people also means protecting their fertility, a very important action within the broader scope of the interventions aimed at reducing the drop in the birthrate affecting modern society. Despite few exceptions, the prevention and early diagnosis of the andrological conditions have been neglected worldwide for too long. This has favored an increase in the incidence and prevalence of diseases that are otherwise easy to prevent and treat if diagnosed early.

The data collected during screening procedures in young males show that <5% receive an andrological examination before the age of 20. Female patients of the same age adhere to gynecological screening tests with decidedly higher rates. A real “gender discrimination” about prevention [4].

This leads to an increase in undiagnosed andrological diseases that remain so until adulthood when the treatment becomes more complex for the patient and more expensive for the national healthcare system.

Therefore, it is necessary to promote awareness on this social issue: undergoing regular and well-timed andrological checkups is essential for the early diagnosis of andrological conditions as well as for the general health of men’s sexual and genital functions.

This point in mind, in order to safeguard the reproductive and sexual health of young men, the synergic approach involving pediatricians, general practitioners, doctors at family planning clinics, and andrologists for the adults plays a key role together with the implementation of territorial networks integrating the know-how and expertise of all these health professionals.

This is especially true in the extremely vulnerable period of life generally ranging from 11 to 18 years of age, when young male patients experience the transition to adult life and maturity from the reproductive and sexual point of view.

All this can be achieved also increasing the social awareness on the matter via systematic information and education of the population thanks to campaigns and primary prevention interventions. To this end, research and study of andrological diseases in the pediatric-adolescent patients are crucial, especially research, whose main aim is to anticipate the treatment of all those conditions that can alter the fertility potential of men.

These are the grounds for this study, which compares good clinical practices worldwide for the preservation of male fertility in young patients by comparing the results with the evidence from the scientific research carried out on the treatment of male infertility.

In the last 40 years, the number of spermatozoa in the semen of male patients of childbearing potential has decreased by more than a half [5].

Incorrect lifestyles, pollution, and poor prevention are the main causes of a dramatical drop in the male fertility rates. According to the latest international

reports, the rate of male infertility among the couples who seek advice from specialized centers to bear a child is 30–35%, and age is not the only liable factor; correctable causes include varicocele, which accounts for 30–35% of cases, and evidence of previous untreated or poorly followed cryptorchidism (5%) [5–7].

Medically assisted procreation is suggested as one solution to the human and social problem of sterility. But, as reported by many authors, can assisted procreation be considered as a suitable therapy?

In many countries, assisted procreation is funded from public health insurance. Without this coverage, it would be used much less frequently. What is then more important? The treatment of sterility or the increase in the birthrate? The answer to this question is manifold.

One of the reports by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) re-established that over 1 million ART cycles were performed worldwide in 2002, with a progressive increase compared to the previous years. The progressive increase shows how research and clinical medicine are drastically moving away from the real investigation of infertility [6–8].

The costs associated with the ART can be divided into direct and indirect costs; the direct costs, which vary according to the mother's age, are those necessary to “guarantee” a pregnancy, from the medically assisted treatment to childbirth. The indirect costs include the costs directly related to childbirth, to a possibly premature birth, to twin pregnancies, to the management of any complications, and to the management of chronic diseases of the newborn child and of the mother as well [7–9].

Obviously, the average direct cost of each procedure is calculated by dividing the total number of procedures performed per year by the number of live births. These costs are country-related, with variations of up to tenfold values; direct ART treatment costs show considerable variations among countries, with the USA standing out as the most expensive and Northern European countries and Japan as the least expensive countries. For example, reports show that the costs per live birth are similar for ages 24 (€17,000) and 33 (€ 18,500), after which they begin to increase, with the cost per live birth reaching € 54,000 at age 42.

Indirect costs, especially when associated with multiple gestations, vary from country to country: in 2004 such costs ranged between € 24,377 for a singleton pregnancy and € 35,042 for a twin pregnancy up to 27 days after birth [6–9].

The first international report on the results of assisted medical procreation (AMP) was published in Paris in 1991 on the occasion of the 7th World IVF Congress. From a scientific point of view, the role of international reports is to monitor the number of procedures as well as to study the efficacy of the treatments indicated.

Every year the procedure registers are updated. The recorded data show a constant increase in these procedures with a steady increase in live births. The latest data, published in 2018 and referring to 2011, show that approximately 1.6 million procedures were performed with approximately 400,000 births worldwide. These figures allow to calculate the costs per year for the national healthcare systems [7–9].

2. Literature searching

This research was performed by taking into consideration two aspects separately: infertility and pediatric andrological diseases associated with infertility. Browsing the most important engines for scientific research (PubMed, Scopus, Google Scholar), several keywords were considered: infertility, male, semen,

adolescent, varicocele, undescended testes, cryptorchidism, hormone, and assisted medical procreation (**Table 1**).

We searched with association like: adolescent and infertility; varicocele and semen, etc.

A number of papers and number of the most important associations are explained in the table.

Some considerations are essential: the literature regarding medically assisted procreation should be considered only from 1990 onward, and, from a strictly epidemiological point of view, also for varicocele some distinctions should be made. Varicocele seems to have a clear phenotypic trend, for which it is possible that in some countries the prevalence of the disease is lower than in others, justifying a paucity of literature on this topic. However, when comparing the origin of scientific publications on pediatric varicocele and cryptorchidism, Europe and North America cover about 70% of the overall publications worldwide, reaching 80% of the published literature about infertility and assisted medical procreation. Asia and Africa, on the contrary, show poor preventive research while favoring the research on assisted medical procreation.

The analysis of the data offers some interesting insights:

- 1. Most of the literature on the topics of this research was published after the year 2000, with the two maximum rates of 84 and 79% for medically assisted procreation. This can be reasonably associated with the widespread use of the procedures after the 1990s. If such figures are correlated to the other percentages found, they also show how the focus of scientific research has slanted toward the treatment of infertility rather than its prevention.
- 2. In absolute numbers, the conditions directly associated with infertility are less studied than the treatment with medically assisted procreation.

Group	Key	Total	>2000 % of paper	Statistical comparison per group
1	Infertility-male	46103	26296 (57%)	1/2: p < 0.05
2	Varicocele	5292	2788 (52%)	1/3: p < 0.05
3	Undescended testes	10245	4250 (41%)	1/3: p < 0.05
4	Assisted reproduction	25399	20309 (79%)	1/4: p < 0.05
5	V-adolescence/ pediatric age	1396 147 (real pediatric- adolescent age-range with follow-up)	776 (55%)	2/5: p < 0.05
6	Infertility-U	1195	676 (56%)	6/3: p < 0.05
7	Infertility-semen	11289	6556 (58%)	1/7: p > 0.05
8	Assisted medical procreation	6701	5635 (84%)	1/8: p < 0.05
9	Infertility-VAR	2429	1349 (55%)	1/9: p < 0.05

Statistical analysis: Statistical analysis was performed using the student t-test. Significance value was set at p < 0.05. Associations: varicocele and pediatric age/adolescence; infertility and undescended testes; infertility and varicocele; statistical comparison between groups: chi-square test comparing number of total paper published and paper published after 2000 per each -group and sub groups.

Table 1.
Data from the research: number of papers published per disease and with multiple associations.

3. A comparison between varicocele and cryptorchidism, namely, the two main male infertility diseases, shows that although varicocele is the first treatable cause of infertility, it is not as much investigated as cryptorchidism, accounting for <5% of the curable causes of infertility. From a purely numerical point of view, cryptorchidism is studied more than varicocele, with varicocele being more investigated after the year 2000. This means that long-term studies on varicocele have been done only in the last 20 years.
4. A comparison between group 1 (infertility and male), which is the most represented in terms of number of publications pre- and post-2000, and all the other subgroups points out that the “infertility and semen” subgroup is the only comparable group within the main scope of the survey. This indicates that most of the studies on male infertility do not investigate the causes leading to these conditions, because they focus only on their effects
5. The correlation between infertility and varicocele offers some insights: while in numerical terms, there is little investigation of varicocele in association with infertility, which is one of its effects; more is studied about its treatment (surgical treatment, percutaneous treatment, etc.). It is important to report that since 2000, only 147 papers focused on pediatric-adolescent varicocele and its management with a long time follow-up (>3 years).

3. Pediatric varicocele

3.1 Focus about pediatric varicocele: the first infertility-related and treatable andrological disease

About this specific topic, where varicocele is the first treatable cause of infertility in adulthood, we found that a total of 625 articles was published since 2000, matching the mentioned criteria; after our selection only 147 articles resulted providing innovative topics in the pediatric range. As a first consideration, we can state that most publications concentrate in Europe, Asia, and North America (the USA being by far the most represented in North America). The percentage of pediatric works is 27.0% being above average in Europe and North and South America. Asia has a considerable number of published articles even though the percentage of pediatric ones is far below average. Africa and Oceania have, respectively, 2 and 1 pediatric articles.

Then we analyzed the main topic and secondary topics of the selected articles. Prevalence of different categories in each continent was summarized, and the main subjects for Europe are surgical technique, videolaparoscopy, and diagnosis; for North America, surgical technique, diagnosis, and endocrinology; and for Asia, video laparoscopy, endocrinology, and screening.

South America includes 10 articles discussing mainly about fertility and semen analysis, being the only region in which this topic appears to be central. Africa had only two publications in the pediatric field, centered on diagnosis and non-operative treatment. The only pediatric publication published in Oceania was centered on video laparoscopy.

Overall prevalence of topics in the discussed articles was considered as well, and we found that in North America and Asia follow-up prevails as a concomitant topic in many articles, together with complications and relapses. Another topic strongly represented in these regions is endocrinology. On the other side, Europe maintains topics that mainly represented surgical technique and videolaparoscopy, accounting

for about 50% of all topics, and then diagnosis is still present, showing little difference between main topic and all mentioned topics in the publications.

Eventually, a study of the topics and their prevalence over years was performed to see the trend of interest. A significant trend in publications could not be evinced, neither overall nor for single continent. Publication numbers by year underwent cyclic changes over the last 20 years with a peak in 2008 including 16 publications about pediatric varicocele.

A natural comment to the number of publication is the fact that pediatric articles, focusing on pure research, account for <1 third of overall articles about varicocele. This could be due to the fact that historically varicocele is considered as an adult pathology; thus not enough interest is found in its pediatric side. Different series of studies report a higher prevalence of varicocele in adult population than in pediatric one. However it must be taken into account the lack, in almost all countries, of pediatric screening programs for varicocele that could give a strong bias about the exact prevalence of the pathology in pediatric population. Moreover the study of varicocele related to infertility is considered more imminent in adult life, when looking for paternity that during adolescence when study of future fertility may seem premature. In fact many studies on varicocele are performed retrospectively when the patient in adult life has not the possibility to become father (see table).

Concerning the major topics of the publications, in the most represented continents, the first interest of research is surgical technique, may it be traditional surgery or videolaparoscopy technique. We can also see that in the first three majorly represented topics and figures either screening or diagnosis this reflects an attention of research to detection and treatment rather than to follow-up or prevention of infertility. Other topics were only minimally represented. It must be stated that healthcare organization of each single country may influence the topics and publications: in fact screening would not be so represented in countries with private healthcare or, on the other hand, countries with increased population density would feel less important the problem of infertility. The prevalence of varicocele according to the literature remains constant in different ethnic groups; thus, differences in publication do not reflect a difference of entity of the disease but rather a different contribution to publications.

In South America the research group for the published articles is the same, and the works represent mainly an evolution of the same study focusing on semen analysis, metabolomics, infertility pathophysiology, and endocrinology.

The three most prevalent topics in North America and Asia underline an attention to study the evolution of the pathology in time even after treatment and to evaluate if the outcomes of surgical treatment meet the standards for good practice. Articles discussing endocrinology often evaluate testicular volume at diagnosis and follow catch-up growth after surgery, trying to give an indication of the best timing to prevent infertility. On the other side, the spectrum of topics in Europe reflects poor attention to prevention of infertility and follow-up after surgery.

Of particular interest is that there is no increasing trend during the years despite an increase in the trend of publications about overall causes of infertility and medically assisted procreation. In fact in delivering a PubMed research, it appears that publications about MAP are more than 30 times higher than those about varicocele.

We must report the fact that Asia appears abundantly below average, but a strong bias is given that the fact that many publications from China were in original language [10–17].

The same applies to the correlation between undescended testes and infertility if compared to the studies on cryptorchidism alone. Both associations between infertility and disease show a progressive percentage increase in the total number of studies.

4. Final considerations

This research is intended as a warning to the countries worldwide: when talking about fertility, it is right to give a couple the chance to access medically assisted procreation; consequently, scientific studies to improve its outcomes are reasonable. International reports are therefore necessary and should foster research with increasing outcomes. More space should also be given to investigate and prevent male fertility diseases starting from the pediatric age, especially when they might impair the patient's future fertile potential [18].

All those involved in the pediatric treatment area should be stimulated to act toward this goal, and each country should bear the responsibility of promoting and financing andrological screening campaigns. At the international level, there are still few opportunities, in terms of funds and staff, for the adolescents to receive andrological counseling. This is then the bottom line: Is medically assisted procreation the cure to one or more diseases, or is it the answer to the lack of a social support network?

When talking about couple infertility, male causes account for about 35–40%, among these, varicocele figures as the first [19].

Thus collective interest, research efforts, and healthcare funding aim to study couple infertility at the time of inability of procreation, correction of varicocele in adult age, and medically assisted procreation. This choice is taken despite the increased risk of chronic irreversible damage of treating varicocele and other pediatric andrological diseases in adult age and despite the costs and risks of MAP with the additional risk of failure of medically assisted procreation.

In conclusion, the research effort and the capital invested in prevention of infertility are not balanced with respect to efforts and investments relied into medical assisted procreation.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

AMP	Assisted medical procreation
ART	Assisted reproductive technology

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Author details

Zampieri Nicola*, Bianchi Federica, Patanè Simone, Vestri Elettra
and Camoglio Francesco Saverio
Woman and Child Hospital, Azienda Ospedaliera Universitaria Integrata,
Department of Surgery, Dentistry, Paediatrics and Gynaecology, Paediatric Fertility
Lab, University of Verona, Verona, Italy

*Address all correspondence to: dr.zampieri@libero.it

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