Douglas T. Carrell · Peter N. Schlegel
Catherine Racowsky · Luca Gianaroli
Editors

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We dedicate this volume of Biennial Review of Infertility to those who receive far too little credit for their essential roles in assisting infertile patients and clinicians, including nurses, medical assistants, embryologists, andrologists, and office personnel. Your compassion, dedication, and skills make all the difference.

Preface

This is the fourth volume of Biennial Review of Infertility (BRI). The objective of this series is to bring to clinicians, embryologists, andrologists, scientists, laboratory technicians, and ancillary healthcare providers of infertile patients a timely collection of topics that are cutting edge and written by thought leaders in the field of infertility care and research. While that goal is daunting, the previous volumes of Biennial Review of Infertility have succeeded and been valuable to the community. We are excited to continue with volume 4 of Biennial Review of Infertility.

Volume 4 continues the tradition of providing reviews and commentaries on the cutting edge of male reproductive medicine, female reproductive medicine, and the field of assisted reproduction technologies (ART). Chapters included in this volume of BRI cover topics such as the use of stem cell technologies in male infertility therapy, molecular mechanisms and causes of reduced oocyte quality associated with aging, the use of time-lapse imaging in the ART laboratory, a critical review of the use of acupuncture during ART, and the use of the Internet in clinical practice to benefit patients and the clinic. That is certainly a diverse range of chapters, which highlights the breadth of topics that the clinician encounters in daily practice. As always, those selected to present the topics are unquestionably leaders in the field and have provided clear and thought-provoking reviews.

While science sometimes moves forward in incremental leaps, often it is the gradual addition of data that provides a slower path forward. For that reason, as well as the complexity of the problems studied, best clinical practice can sometimes be gray and meandering, with thoughtful and honest clinicians disagreeing about the best therapy for a given problem. For that reason, we continue with the "Controversies" section of BRI in this volume. This section is likely the most popular section of the series, since it provides clear and distinctly different conclusions from well-respected thought leaders. In BRI4, Eli Adashi and Dmitry Kissin argue that elective single embryo transfer should be the standard of care for ART patients, while G. David Adamson presents the arguments for the alternative conclusion. Second, Darius Paduch and Peter Schlegel debate the pros and cons of early treatment of the adolescent patient with Klinefelter Syndrome. Lastly, the controversial topic of the use of dietary supplements in the ART patient is critically reviewed.

We are grateful for the willingness of the authors to share their expertise. In order to get fresh and cutting-edge information, Biennial Review of Infertility operates on a tighter deadline schedule than most books. The authors' efforts

are appreciated. We, as co-editors, are also grateful to the readers of BRI4 for your continued desire to understand complex topics and to use our volume to assist in providing the best care possible to patients. We are confident that this volume of Biennial Review of Infertility will also help stimulate new ideas and perspectives for future clinical and basic science studies.

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Part I

Male

The Epidemiology of Male Infertility

1

John R. Gannon and Thomas J. Walsh

1.1 Identifying Infertility

Infertility is defined as the inability for a healthy couple to conceive after 12 months of regular, unprotected intercourse [1]. Infertility affects approximately 20 % of couples and has been recognized as a disease according to the Americans with Disabilities Act of 1998 [2]. This distinction and recognition as a disease may improve awareness and require that infertility be identified, registered, and treated.

Several characteristics make the epidemiology of infertility challenging to study. Male infertility is not a reportable disease and is therefore not identified or captured in databases such as the Surveillance, Epidemiology, and End Results [SEER] Program that tracks new cases of cancer. Male infertility is diagnosed and treated in the outpatient clinical setting; therefore, limited numbers of cases are captured through hospital admission and billing codes. Fertility care is often not covered by health insurance, and out-of-pocket costs are not identified in the claims data of most large insurance consortiums. Additionally male factor infertility is frequently treated empirically with in vitro fertilization. This focus on the female partner further limits the identification of male factor infertility cases.

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The only existing large-scale database with the goal of identification of male factor infertility is provided by the Center for Disease Control and Prevention. The SART database tracks the utilization of assisted reproductive technology [ART]. While useful, such data has historically provided very limited details regarding the causes of male infertility [3].

The National Survey of Family Growth (NSFG) provides some population-based data on male factor infertility. The purpose of the survey is to obtain national estimates of pregnancy, infertility, contraception, marriage, divorce, and further information. This periodic survey initially was limited to women during the 1970s and 1980s, but starting with the sixth cycle in 2002, men were included. The use of infertility services was identified by one question, "Have you been to a doctor to talk about ways to help have a baby together" [4, 5]? A study published in 2013, examining data from the NSFG, revealed that 18–27 % of men in couples experiencing infertility were not evaluated for male factors [4]. An additional study by Hotaling et al. published in 2012 examined data from the NSFG cycle 6; this study found that marital status and education level were associated with those who sought care at a fertility center [5]. These studies suggest that the rate of male infertility may be underestimated, and studies that report data on male infertility from large, tertiary, referral centers may not be generalizable to all infertile men (Table 1.1).

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Table 1.1 Population-based studies describing infertility

Study title	Author	Year	Population	Couple infertility (%)	Male factor (%)	Female factor (%)
Estimation of the prevalence and causes of infertility in Western Serbia	Philippov et al. [8]	1998	2,000 married women; 186 couples	38.70	6.40	52.70
High prevalence of male infertility in Southeastern Nigeria	Ikechebelu et al. [9]	2003	314 couples	25.80	42.40	20.70
Clinical patterns and major causes of infertility in Mongolia	Bayasgalan et al. [10]	2004	430 couples	18.80	25.60	45.80
Incidence and main causes of infertility in a resident population (1,850,00) of three French regions	Thonneau et al. [6]	1991	1,686 couples	30	20	39

1.2 Incidence and Prevalence of Male Infertility

Male infertility may be caused by numerous factors including genetic causes, poor semen quality, medical disease, hormonal aberrations, or other unknown causes [2].

Several studies have sought to quantify the burden of male factor infertility [6–9]. Findings from these studies are difficult to interpret due to methodological flaws, and their generalizability is limited due to the specificity of the populations studied; however, they provide some information on the epidemiology of male infertility.

A study published in 1998 in Western Siberia, conducted on 2,000 married women using the World Health Organization questionnaire, found the prevalence of couple infertility to be 16.7 %. The prevalence of male infertility was 6.4 %, with an unusually high rate of female factor infertility (nearly 53 %). The rate of female factor infertility was determined to be secondary to high postpartum complications and abortions [8].

A retrospective review conducted on 314 couples evaluated from 1997 to 1998 in Southeastern Nigeria suggested an unusually high rate of male infertility at 42.4 %. High rates of male infertility in this study were attributed to sexually transmitted disease and inadequate treatment for these conditions [8, 9].

A study conducted by Thonneau et al., "Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988-1989)," examined three defined geographic regions in France. This study revealed male factor infertility in 20 % of the 1,686 couples studied in a specific French region in 1991. Despite the title of Thonneau's study suggesting *incidence*, the authors in fact quantified the *prevalence* of male factor infertility in this study population given that this study was conducted at a single point in time (cross-sectional study design) [6].

A retrospective study conducted in Mongolia and published in 2004 found male factor accounted for 25.6 % of all infertility. This study, like the prior study from 2000 in Western Siberia, showed a high prevalence of female factor infertility, 46 %. Within this specific study, this high rate was felt to be secondary to pelvic inflammatory disease [10].

Many of these studies claim to describe prevalence and incidence but instead report case series data, without a firm understanding of the base population from which the cases arise [11]. None of these studies clearly define the incidence of male infertility given that they fail to report on new cases within a specified time period. These studies were conducted in different geographic regions, and the dramatic differences in the statistics they report underscore the importance of geographic variation and the inability to generalize their findings to other populations. To further add to the differences among these studies and their limitations, the urologic disease project in America in 2007 sought to consolidate the available literature in an attempt to understand the burden of disease. The authors of this study searched multiple databases

including SART, the national survey of ambulatory surgery, VA administration, and others. Ultimately they concluded that male factor infertility might be present in 30 % of all infertility cases, accounting for methodology and selection bias in these prior studies [3, 12].

1.3 Secular and Birth Cohort Trends

Two methods used to describe a disease, such as male infertility, are secular and birth cohort trends. Secular trends describe the change in incidence of a disease over time. Secular trends have been used in studies of fertility to inform how changes in environmental exposures have altered the incidence of infertility within a given population [6–9]. Birth cohort trends describe changes in a disease associated with the generation in which an individual is born. Birth cohorts may be used to compare differences in a disease between generations of individuals. Secular and birth cohorts have been associated with differences in birth rates, semen analyses, and fecundity [1, 13, 14].

Several studies have sought to use birth cohort trends as a means of understanding whether or not infertility rates have changed over time in response to the ever-changing environment in which we live [14]. While there is no data that effectively identifies the incidence of male infertility related to the generation in which a patient was born, data does exist pertaining to semen analyses. A semen analysis is an easily replicated test, which some studies have sought to use as a proxy for male infertility. While there is no direct correlation between a normal semen analysis and fertility, this information is valuable in the assessment of the epidemiology of male factor infertility [14].

In 1992 Carlsen et al. made one of the first attempts to quantify changes in semen analyses in men, examining 61 studies, with nearly 15,000 men and their respective semen analyses from 1938 to 1991. Carlsen's linear regression analysis showed a significant decrease in sperm concentration from a mean of 113 million/mL to a mean of 66 million/mL and a decrease in semen volume from 3.4 mL to 2.75 mL [13]. From this, the authors concluded that semen quality was declining over time.

Fisch, when reviewing these studies, suggested significant flaws with Carlsen's initial analysis. Fisch evaluated the same 61 studies; however, they limited their analysis to larger studies with greater than 100 semen samples. Their review found trends related to geographic variations, with lower sperm counts observed in later years in more developed countries, when compared to earlier specimens [15]. Further examination of the initial 61 studies found additional study limitations such as variable methods of semen collection and no controls for confounding variables such as drug use, smoking, or abstinence [16].

In a repeat analysis of Carlsen's data, Swan and other investigators in 1997, controlled for abstinence, age, collection method, and men with proven fertility. These authors' findings demonstrated significant declines in sperm concentration in the USA, Europe, and Australia [17]. Fisch and Braun conducted a systemic review of 35 semen analysis studies. A total of eight studies accounting for 18,109 men suggested a decline in semen quality and quantity. Twenty-one of the studies examined, with 112,386 men, appeared to show no significant change in semen quality. Six studies, 26,007 men, showed results that were not interpretable due to conflicting or ambiguous results [16].

While we may continue to examine semen analyses using our epidemiologic methods, there is no clear evidence a decline in semen quality exists.

1.4 Geographic Variation

While geography alone is unlikely to put men at risk for infertility, it may be a surrogate marker for other exposures or cultural differences that increase risk. As such, geography is considered a key variable to enable better understanding of disease. Capturing geographic variation in the diagnosis and treatment of male infertility is challenging. There are a limited number of fertility centers, which are often clustered in metropolitan areas, thereby limiting access to care for those from rural areas. The geographic constraints

limit our insights by limiting patient's access to identification, evaluation, and treatment.

In spite of these limitations, several studies corroborate the extent of geographic variation in male fertility. The most recent review of the National Survey of Ambulatory Surgery in 2009 revealed that there was an increased prevalence of outpatient infertility evaluations conducted in the Northeast. The South, Midwest, and finally the West followed the Northeast in the prevalence of outpatient evaluations respectively [18]. These differences may be attributed to nationwide insurance trends as well as increased access to infertility clinics in the Northeast.

In a study performed in 2003, Swan and colleagues examined semen analysis performed in four cities representing each geographic region previously mentioned: Northeast (New York, New York), Midwest (Minneapolis, Minn.), West (Los Angeles, Calif.), and South (Columbia, Miss.). Examining 512 samples, sperm parameters (concentration, motility) were reduced in the semirural and agricultural areas of Mississippi and Minnesota [18]. Additional reviews support these findings. Fisch and collaborators described differences in sperm concentrations between numerous countries, both industrialized and not [12, 14, 16, 17]. The lower semen parameters seen in rural areas were attributed to genetic and environmental factors, including sexually transmitted infections, pesticide use, environmental toxins, and other contributing factors.

1.5 Racial Variation

Studies examining racial variation in male factor infertility are sparse. The NSFG was reviewed in 2013, by Eisenberg, and demonstrated that Caucasian men are more likely to undergo infertility evaluation [4]. Conversely, data from the US Veterans administration suggests that Hispanics followed by African Americans and Caucasians have the highest frequency of undergoing treatment for male factor infertility [3]. The VA study however did not offer a clear cause of what appeared to be a discrepancy among those undergoing treatment.

Examining a large, diverse population of 1.5 million men older than 18 in the Kaiser Permanente of North California (KPNC) network in 2008, Walsh and colleagues described 30,000 men who underwent evaluation for infertility by semen analysis. Overall, 36 % of these men evaluated were found to have abnormalities in their semen analysis [19]. Interestingly, 49 % of African American men were found to have abnormalities on their specimen, while 37 % of Caucasian, 38 % of Asian 38 %, and 39 % of Hispanic men were found to abnormalities [19]. While this study does not inform whether or not race is etiologically involved in fertility or poor semen quality, it suggests that there is significant racial difference in the proportion of men with abnormal semen quality.

A 2001 study conducted by Costabile provided further insight into the association between race and male infertility. This study of a single provider, working in a no-cost, military healthcare system, described the age, race, length of subfertile period, medical history, and lab evaluations of men seeking fertility care. This study found no significant racial differences among men undergoing infertility evaluations [11].

1.6 Conclusions

Epidemiology describes the occurrence and impact of disease in a defined population. Understanding the epidemiology of any given disease may help to identify individuals who are at risk and enable or expedite the identification of causes or treatments. A better understanding of the burden of infertility will allow improvements in both the counseling and treatment of male factor and female factor infertility.

The epidemiology of male infertility is difficult to study. Male infertility is not a reportable disease and is not tracked by a dedicated database. The lack of insurance coverage and treatment in an outpatient setting leads to poor identification and tracking of men undergoing fertility care. Empiric treatment related to female infertility additionally may lead to an underestimation of male factor.

The incidence of male factor infertility has not been determined. The prevalence of male infertility has been estimated in heterogeneous studies that are limited and difficult to apply to the population as a whole. Further studies linking a decline in semen parameters and male infertility are inconsistent and often contradictory. Male fertility appears to be influenced by many factors including geography, race, and environment.

In spite of the challenges we face and the present lack of data, the future of male infertility epidemiologic research holds promise. The creation of a longitudinal cohort accruing all men with infertility will be pivotal as such data could include variables such as demographics, socioeconomic status, and quantification of putative environmental factors. The accumulation of such information will improve treatment and outcomes for men with male factor infertility.

References

1. Skakkebaek NE, Jorgensen N, Main KM, Rajpert-De Meyts E, Leffers H, Andersson AM, Juul A, Carlsen E, Mortensen GK, Jensen TK, Toppari J. Is human fecundity declining? Int J Androl. 2006;29(1): 2–11.
2. Sabanegh Jr ES, Agarwal A. Male infertility. In: Wein A, editor. Campbell-Walsh urology. Philadelphia, PA: Elsevier Saunders; 2011. p. 616–47.
3. Meacham RB, Joyce GF, Wise M, Kparker A, Niederberger C. Urologic diseases in America P. male infertility. J Urol. 2007;177(6):2058–66.
4. Eisenberg ML, Lathi RB, Baker VL, Westphal LM, Milki AA, Nangia AK. Frequency of the male infertility evaluation: data from the national survey of family growth. J Urol. 2013;189(3):1030–4.
5. Hotaling JM, Davenport MT, Eisenberg ML, VanDenEeden SK, Walsh TJ. Men who seek infertility care may not represent the general U.S. population: data from the National Survey of Family Growth. Urology. 2012;79(1):123–7.
6. Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, Lopes P, Tabaste JM, Spira A. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Hum Reprod. 1991;6(6):811–6.
7. Gunnell DJ, Ewings P. Infertility prevalence, needs assessment and purchasing. J Public Health Med. 1994;16(1):29–35.
8. Philippov OS, Radionchenko AA, Bolotova VP, Voronovskaya NI, Potemkina TV. Estimation of the prevalence and causes of infertility in western Siberia. Bull World Health Organ. 1998;76(2):183–7.
9. Ikechebelu JI, Adinma JI, Orie EF, Ikegwuonu SO. High prevalence of male infertility in southeastern Nigeria. J Obstet Gynaecol. 2003;23(6):657–9.
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11. Costabile RA, Spevak M. Characterization of patients presenting with male factor infertility in an equal access, no cost medical system. Urology. 2001;58(6):1021–4.
12. Winters BR, Walsh TJ. The epidemiology of male infertility. Urol Clin North Am. 2014;41(1):195–204.
13. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ. 1992;305(6854):609–13.
14. Fisch H, Goluboff ET, Olson JH, Feldshuh J, Broder SJ, Barad DH. Semen analyses in 1,283 men from the United States over a 25-year period: no decline in quality. Fertil Steril. 1996;65(5):1009–14.
15. Fisch H, Goluboff ET. Geographic variations in sperm counts: a potential cause of bias in studies of semen quality. Fertil Steril. 1996;65(5):1044–6.
16. Fisch H, Braun SR. Trends in global semen parameter values. Asian J Androl. 2013;15(2):169–73.
17. Swan SH, Elkin EP, Fenster L. Have sperm densities declined? A reanalysis of global trend data. Environ Health Perspect. 1997;105(11):1228–32.
18. Swan SH, Brazil C, Drobnis EZ, Liu F, Kruse RL, Hatch M, Redmon JB, Wang C, Overstreet JW. Study for future families research G. Geographic differences in semen quality of fertile U.S. males. Environ Health Perspect. 2003;111(4):414–20.
19. Walsh TJ, Schembri M, Croughan MS, Smith JF, Smith JF, Jones KT. Epidemiologic characteristics of men evaluated for infertility in a large, pre-paid insurance plan. Fertil Steril. 2008;90(Suppl):S63.