CHAPTER 14

Male Infertility

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INTRODUCTION

Male infertility presents a particularly vexing clinical problem. While the patient's semen may seem to be the target for diagnostic and therapeutic interventions and analysis, a positive outcome is in fact manifested by another person, a mother, giving birth to a child. And whereas presence of offspring is the ultimate proof of male reproductive health, the manner in which outcomes are expressed in this area are perhaps the most sensitive in medicine to probabilistic statements. For example, outcomes of artificial reproductive techniques are expressed in probabilities, such as the "take-home baby rate," the likelihood per intervention that a particular therapy will result in a live birth. For these reasons, epidemiologic statements regarding male reproductive dysfunction present formidable challenges, and the patients undergoing diagnosis and treatment for infertility are often understandably confused.

DEFINITION AND DIAGNOSIS

Infertility is typically defined as failure to conceive within a certain period of time. For the male, this definition is particularly problematic, as it relies on an outcome for his female partner, who may have reproductive issues of her own. *Fecundability* is the term used for the probability of a woman in a sexually active couple becoming pregnant per menstrual cycle without contraception. The measurement of fecundability is subject to a number of biases, including the prevalence of contraception prior to intended conception and how previous pregnancies are counted in a study design model (1). These biases may skew estimates of fecundability by as much as 30% to 100% (1).

It is customary to define infertility clinically as the inability of a couple trying to conceive to do so within one year. This may make the usual definitions of *prevalence* and *incidence* somewhat confusing in this context. In this chapter, we use *incidence* as it is classically defined—a proportion per unit time. However, many authors use *prevalence* to describe the percentage of couples failing to conceive after one year.

As detailed below in the section on prevalence and incidence, approximately 15% of sexually active couples without contraception do not conceive within one year. The difficulty inherent in defining infertility in this manner is obvious: some couples without reproductive dysfunction who wish to conceive fail to do so by probability, or simple bad luck, while others harbor reproductive-system pathologies that prevent conception. If a good assay were available for male reproductive function, independent of the female, a sensible and practical definition of male infertility would be "the condition of the subset of males with a positive assay within the set of couples that fail to conceive within one year." Such an assay does not currently exist. The most common initial assessment of male reproductive potential, the "bulk semen assay," is notoriously poor. The raw data from MacLeod's seminal 1951 publication indicate that the receiver operating characteristic (ROC) curve area for semen density to predict infertility is 0.59, and for that

Table 1. Codes used in the diagnosis and management of male infertility

Males 18 years or older with one or more of the following:	
ICD-9 diagnosis codes	
456.4	Scrotal varices
606	Male infertility
606.0	Azoospermia
606.1	Oligospermia
606.8	Infertility due to extratesticular causes
606.9	Male infertility, unspecified
CPT procedure codes	
52347	Cystourethroscopy with transurethral resection or incision of ejaculatory ducts
54500	Biopsy of testis, needle (separate procedure)
54505	Biopsy of testis, incisional (separate procedure)
54900	Epididymovasostomy, anastomosis of epididymis to vas deferens; unilateral
54901	Epididymovasostomy, anastomosis of epididymis to vas deferens; bilateral
55200	Vasotomy, cannulization with or without incision of vas, unilateral or bilateral (separate procedure)
55300	Vasotomy for vasograms, seminal vesiculograms, or epididymograms, unilateral or bilateral
55400	Vasovasostomy, vasovasorrhaphy
55530	Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure)
55535	Excision of varicocele or ligation of spermatic veins for varicocele; abdominal approach
55540	Excision of varicocele or ligation of spermatic veins for varicocele; with hernia repair
55550	Laparoscopy, surgical, with ligation of spermatic veins for varicocele
55870	Electroejaculation
74440	Vasography, vesiculography, or epididymography, radiological supervision and interpretation

of motility, 0.50, literally no better than flipping a coin (2). Fifty years later, in a large study by Guzick et al., the ROC area for semen density was 0.60; for motility, 0.59; and for morphology, 0.66—none of which inspires confidence in the predictive ability of the bulk semen analysis (3). In fact, these investigators, using the findings from a classification and regression tree (CART) analysis, suggest using two thresholds for each bulk seminal parameter to counsel male patients about their reproductive potential (3).

Table 1 presents the diagnosis and treatment codes for the analyses detailed in this chapter. Diagnosis codes referring to laboratory abnormalities (such as oligospermia) are mixed with codes deriving from identifiable physical conditions (such as varicocele) that may result in laboratory abnormalities. Such overlapping diagnosis codes plague any analysis of available data.

Table 2 lists conditions identified in men presenting for evaluation of infertility in studies of distribution of diagnoses from 1978 and 1997 (4, 5). It appears that in the 20 years between these two reports, more diagnoses became available, and more risk factors for infertility were identified. Interestingly, the proportion of men labeled with idiopathic infertility remained similar, at approximately 25% in 1978 and 23% in 1997.

For the clinician and researcher, a sensible method of classifying reproductive dysfunction is to separate problems into medical and surgical, with the latter including anatomic defects. Genetic conditions such as hermaphroditism or congenital absence of the vas deferens may be manifest in either category. Both medical and surgical ailments may or may not be observed in abnormalities in the bulk semen analysis; therefore, the practice of basing a primary diagnosis on bulk seminal anomalies for the purposes of data analysis is discouraged. (We note that clinicians commonly make an initial diagnosis based on seminal parameters before clinical evaluation reveals an underlying condition. For example, a case may initially be identified as "azoospermia," and later as "obstruction." While such practice is understandably unavoidable in clinical conduct, it confounds the analyses presented in this chapter.) Medical diagnoses include immunologic conditions such as antisperm antibodies, infectious diseases (which may result in surgical diagnoses if anatomic obstruction ensues), endocrinopathy, gonadotoxin exposure, and systemic illness (e.g., cancer). Surgical diagnoses include ductal obstruction (*ductal* here refers to the entire reproductive anatomic tract), congenital anatomic anomalies, varicocele, and erectile dysfunction. Medical and surgical diagnoses may coexist in the same condition, such as in the congenital anomaly unilateral cryptorchidism, in which the undescended testis exerts an as yet incompletely understood toxic effect on the contralateral descended testis.

What remains in a binary medical and surgical categorization of male reproductive dysfunction are cases of spermatogenic dysfunction (such as hypospermatogenesis, maturation arrest, and Sertoli-cell only syndrome) and specific sperm anomalies

Table 2: Distribution of male infertility diagnoses, 1978 and 1997

Diagnosis	1978[a] Percent (n=420)	1997[b] Percent (n=1,430)
Varicocele	37.4	42.2
Idiopathic	25.4	22.7
Obstruction	6.1	14.3
Female Factor	...	7.9
Cryptorchidism	6.1	3.4
Immunologic	...	2.6
Volume	4.7	...
Agglutination	3.1	...
Viscosity	1.9	...
Ejaculatory Dysfunction	1.2	1.3
Testicular Failure	9.4	1.3
Drug/Radiation	...	1.1
Endocrinologic	0.9	1.1
Infection	...	0.9
Sexual Dysfunction	2.8	0.3
High Density	0.5	...
Necrospermia	0.5	...
Systemic Disease	...	0.3
Sertoli-Cell Only	...	0.2
Ultrastructural Defect	...	0.2
Genetic	...	0.1
Testis Cancer	...	0.1

...data not available.

[a]SOURCE: Adapted from Journal of Urology, 119, Greenberg SH, Lipshultz LI, Wein AJ. Experience with 425 subfertile male patients, 507–510, Copyright 1978, with permission from American Urological Association.

[b]SOURCE: Adapted from Lipshultz LI, Howards SS. Evaluation of the subfertile male. In: Lipshultz LI, Howards SS, eds. Infertility in the male. St. Louis: Mosby-Year Book, Inc., 1997:173–193.

(such as necrospermia), in which other diagnoses are not obvious. With the Human Genome Project completed and the next step of correlating genes with function under way in earnest, these diagnostic quandaries may be resolved as genetic dysfunctions are correlated with specific testicular and sperm pathologies. For the present, these two outlying categories may be considered medical.

RISK FACTORS

While not as dramatic as the decline in fecundability with increasing maternal age, male fertility, according to recent evidence, also appears to decline with age, due to decreased sperm function and accumulating genomic damage (6, 7). Other risk factors for male reproductive dysfunction include gonadotoxins such as chemotherapeutic agents, radiation exposure, and a variety of pharmaceutical agents that act either as direct spermatotoxins or through a steroidal pathway (5). Common drugs known to impair male fertility include cimetidine, sulfasalazine, nitrofurantoin, ethanol, cannabis, and androgenic steroids (5). Whether nicotine results in impaired male fertility is controversial; however, because of its negative effect on erectile function, nicotine use is discouraged in men attempting to impregnate their partners (8). While prior fatherhood is no guarantee of current reproductive health, having produced biological offspring in the past is expected to increase the probability of successful reproduction in the male. A male who does not have biological offspring and who presents for reproductive evaluation is labeled as having "primary infertility," whereas one who is unable to impregnate his partner but who already has biological children is referred to as having "secondary infertility" (5).

TREATMENT

The treatment of male infertility includes therapies targeted to specific medical and surgical diagnoses, empiric pharmacologic agents intended to improve spermatogenesis, and artificial reproductive techniques employed to bypass reproductive barriers in the female genital tract. Often, two or all three types of therapy are implemented simultaneously. Male reproductive medicine and surgery remains one of the most actively evolving areas in urology, with a variety of therapeutic modalities under investigation. The most commonly applied treatments are described in this chapter. For further information, the reader is directed to one of the standard clinical texts such as Lipshultz and Howards' *Infertility in the Male* or Goldstein's *Surgery of Male Infertility* (9, 10).

If the diagnosis is ductal obstruction, (e.g., epididymal, vasal, or ejaculatory ductal), surgical therapy is employed to bypass or relieve the obstruction. For the microscopic ducts of the epididymis and vas, microsurgical technique or, at a minimum, optical magnification is required for optimal reconstruction. Vasal obstruction may be investigated by incision of the vas, injection of dye in the direction away from the testis, or radiography, and also by injection of saline and intraoperative assessment of whether the fluid flows easily or requires substantial pressure, indicating obstruction farther within the abdominal course of the vas deferens. Sites of obstruction amenable to reconstruction are those between the epididymis and the inguinal canal. At present, the usual therapy for ejaculatory ductal obstruction is resection of the ejaculatory duct itself via the transurethral route. The presence of this form of obstruction is initially assessed by transrectal ultrasonography, although surgeons have also described cannulation of the ductal system and injection of dye. Obstruction between the inguinal canal and the intraprostatic ductal system is not currently amenable to surgical reconstruction, and if sperm are present, reproduction must be addressed by testicular sperm retrieval and specialized techniques of *in vitro* fertilization (IVF) with the female partner.

One common form of surgical therapy for male infertility is based on the recognition that varicose veins within the scrotum impair spermatogenesis (11). If microsurgical techniques are employed, the testicular artery may be spared. As spermatogenesis requires approximately 72 to 74 days for completion, patients must wait approximately three months before improvement is evident from such therapies that aim to improve spermatogenesis.

Other forms of surgical therapy include extraction of sperm for use in artificial reproductive techniques if obstruction is not amenable to reconstruction or if spermatogenesis is impaired. Such cases generally present with azoospermia, and surgeons have classically used testis biopsy to determine whether the etiology is obstructive, where spermatogenesis will appear to be normal on biopsy, or spermatogenic pathology. If sperm are present, surgeons typically use biopsy procedures to obtain sperm for artificial reproductive techniques as well. (12). If the etiology is obstructive, sperm may be obtained by percutaneous aspiration of the testis or epididymis, biopsy-style surgical incision of the testis, or microsurgical aspiration from the epididymis. In the case of spermatogenic dysfunction, aspiration yields insufficient sperm, and incision of the testis is required. Schlegel described a microsurgical approach in which the surgeon bivalves the testis and surveys each lobule, extracting dilated tubules; this approach is highly effective for obtaining sperm in cases of azoospermia due to spermatogenic dysfunction (13).

A special case of obstruction is that in which the nerves controlling seminal emission are impaired, such as in paraplegia. Depending on the severity of the neural impairment, patients with this condition may be treated by vibratory stimulation of the penis or by transrectal electrical stimulation (14).

Medical therapy may be either for specific male reproductive disorders or empiric. Specific disorders amenable to medical therapy include endocrine disorders such as Kallmann's syndrome, where maldevelopment of specific neurons in the brain causes abnormalities of smell and insufficient release of pituitary hormones; these cases are treated by hormonal replacement (15). Other, more subtle forms of insufficient pituitary hormonal release may also be treated by direct pituitary hormonal replacement or, if the pituitary dysfunction is not severe, with agents that increase pituitary hormonal release, such as clomiphene citrate. If the patient's estradiol levels are too high, aromatase inhibitors may be prescribed (16). Other forms of specific medical therapy include antibiotics for the infrequent acute identifiable infection that is the sole cause of infertility, and immunosuppression for antisperm antibodies, using agents such as prednisone, which is often used in conjunction with artificial reproductive techniques. For patients who ejaculate sperm retrograde into the bladder, sympathomimetic agents may be employed to increase bladder neck tone. Retrieval of sperm from the bladder for use in artificial reproductive techniques in the female is often required in such cases.

The common condition of too few sperm and/or poor motility on semen analysis, without a specific identifiable medical or anatomic abnormality, may be treated by empiric therapy with agents such as clomiphene citrate used to increase sperm production. Few studies in the body of literature on such empiric treatment are placebo-controlled and blinded. With spermatogenesis taking nearly three months to complete, and thus the duration of medical therapy similarly long, the statistical effect of regression to the mean plagues studies that are not stringently conducted, as improvement may be an artifact of the selected population of patients rather than due to the therapy under study.

Discussion of artificial reproductive techniques employed in the female is beyond the scope of this chapter. However, if sufficient motile sperm are available (generally numbering in the millions), they may usually be placed directly through the cervix into the uterus. Intrauterine insemination (IUI) thus bypasses the cervical barrier. If fewer sperm are available, IVF may be used. In this technique, ova are aspirated from the female and incubated with sperm. Embryos that form are then replaced into the female reproductive tract. In a substantial technological leap, Palermo et al. described a technique referred to as Intracytoplasmic Sperm Injection (ICSI), in which a single sperm is injected into an ovum (17). ICSI is required when sperm are extracted directly from the testis, because the sperm are immature.

PREVALENCE AND INCIDENCE

Both in the literature and to their patients, clinicians commonly cite a 15% rate of couple infertility at one year, and this number is likely not far off the mark. Simmons referred to the 15% rate in 1956 but cited "information from reliable sources" without specific evidence (18). MacLeod referred to a 15% rate in 1971, candidly attributing the figure to "rather hackneyed, but probably reliable statistics in the United States and in all countries where reliable records are kept" (19). In this landmark paper, MacLeod noted the selection bias inherent in assigning responsibilities to each gender, a difficulty that plagues accurate assessment of the incidence of the male component of couple infertility to this day (19). In one of the earlier attempts to assess the rate of infertility in the

United States, the incidence of female infertility was calculated to be between 11% and 30%, depending on parity and marital status (20). However, the study was hampered by selection bias based on whether the couple was trying to conceive, and it did not assess whether subjects had ever tried to become pregnant (20). Page, one of the first to attempt to determine the prevalence and incidence of infertility in a population, computed that a study of 3,500 would be sufficient to reduce the confidence intervals to acceptable levels (21). In 1991, the World Health Organization published tables based on the then-available data (22). Although the incidence of infertility varied somewhat by location, as MacLeod noted 20 years earlier, 15% was a remarkably reasonable assessment (22).

In the 1990s, investigators reported fertility rates from localized regions around the globe. Gunnell et al. followed Page's recommendations and sent questionnaires to more than 3,000 British women (23). If failure to conceive after one year was used as the definition of infertility, the overall incidence was 16.1%, with a 95% confidence interval of 14.6% to 17.6%, again remarkably similar to the oft-cited 15% figure (23). The incidence of secondary infertility was 15.8%, and 26.5% of women were found to be infertile at some time in their reproductive lifespan (23). Philippov et al. reported an overall incidence of infertility of 16.7% for 2,000 married women 18 to 45 years of age in Tomsk, Western Siberia, interestingly close to the rate reported in Somerset (24). Given the diagnoses available in the study, the gender distribution was 38.7% for both partners, 52.7% for the female partner only, 6.4% for the male partner only, and 2.2% undetermined (24). However, the study was hampered by a small male sample (n = 168) and limited male diagnoses (24). Interestingly, of the males studied, 45.7% had abnormal semen analyses, with a 9.1% rate of azoospermia (24). Ikechebelu et al. reported gender-specific infertility rates in 314 Nigerian couples, defining male infertility on the basis of an abnormal semen analysis alone (25). In contrast to the results reported by Philippov et al., a positive male factor alone was found in 42.4% of the couples in the Nigerian cohort, and in 25.8%, the female alone appeared to be responsible (25). A combination of male and female factors was found in 20.7% of the couples, while the cause of infertility was unexplained in 11.1% (25). In almost a mirror image of these findings, Bayasgalan et al. reported data from 430 infertile couples in Mongolia (26). A female factor alone was identified in 45.8% of the couples, while a male factor alone was found in 25.6% (26). In 9.8% of the couples, no demonstrable cause was found in either partner, and in 18.8%, both appeared to be responsible (26). Given the similarity in overall incidence for couple infertility, the variability in these results is most likely due to study methodology and sampling biases rather than local geographic factors. An elegant description of sources of bias in computing the incidence of male infertility is given in a paper by Tielemans et al. (27). It is tempting to speculate that if all biases were accounted for, about one-third of infertility would be due to the female alone, one-third to the male alone, and one-third to both partners.

In the available data on the incidence of infertility, the delivery of medical care related to male infertility is largely confined to the physician office and outpatient surgical settings, as might be expected. Moreover, the dollar amount spent on the management of male infertility appears to be relatively small compared with healthcare expenditures for other disease states. This may be due, at least in part, to the fact that infertility treatment is not often covered by health insurance and thus may be underrepresented in databases that use information provided by health insurance entities. Given these caveats, male infertility does appear to constitute a relatively small percentage of ambulatory healthcare delivery in the United States. According to data from the National Ambulatory Medical Care Survey, which are systematically derived directly from physician encounter forms rather than from insurance providers, although more than 750,000 physician office visits were made for the management of male infertility (as any listed diagnosis) during a

Table 3. Physician office visits for male infertility, 1992–2000 (merged), count, percent

	1992–2000	
	Count	Percent
Total	1,122,162,099	100
Visits for infertility as primary diagnosis	748,498	0.1
Visits for infertility as any diagnosis	792,063	0.1

NOTE: Count and percent based estimated number of adult male visits in NAMCS 19922000.

SOURCE: National Ambulatory Medical Care Survey, 1992, 1994, 1996, 1998, 2000.

Table 4. Inpatient hospital stays for males with infertility listed as primary diagnosis, 1994–2000 (merged), count, rate[a] (95% CI), annualized rate[b], age-adjusted rate[c]

	1994–2000			
	Count	4-Year Rate	Annualized Rate	4-Year Age-Adjusted Rate
Total[d]	797	0.9 (0.5–1.2)	0.2	0.8
Age				
18–34	400	1.2 (0.7–1.8)	0.3	
35+	397	0.6 (0.4–0.9)	0.2	
Race/ethnicity				
White	524	0.8 (0.4–1.1)	0.2	0.8
Other	161	0.7 (0.3–1.1)	0.2	0.7
MSA				
Rural	*	*	*	*
Urban	749	1.0 (0.6–1.5)	0.3	1.0

*Figure does not meet standard for reliability or precision.

MSA, metropolitan statistical area.

[a]Rate per 100,000 is based on 1994, 1996, 1998, 2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US adult male civilian non-institutionalized population.

[b]Average annualized rate per year.

[c]Grouped years age-adjusted to the US Census-derived age distribution of the midpoint of years. Individual age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of missing or unavailable race and ethnicity, and missing MSA are included in the total.

NOTE: Counts may not sum to total due to rounding.

SOURCE: Healthcare Cost and Utilization Project Nationwide Inpatient Sample, 1994, 1996, 1998, 2000.

Table 5. Inpatient hospital stays for males with infertility listed as primary diagnosis, by diagnosis code, count, percent[a]

		Male Infertility ICD-9 Code 606.X		Varicocele ICD-9 Code 456.4	
	Visits for Male Infertility	Count	Percent	Count	Percent
Total	797	145	18%	438	55%
Age					
18–34	400	*	*	223	56%
35+	397	*	*	215	54%
Race/ethnicity					
White	524	*	*	307	59%
Other	161	*	*	*	*
MSA			*		
Urban	749	145	19%	420	56%
Rural	48	*	*	*	*

*Figure does not meet standard for reliability or precision.

[a]Percent of weighted visits for primary diagnosis of male infertility (within each demographic category) with diagnosis code.

NOTE: Counts were too low to report admissions for ICD-9 codes 606.0 (azoospermia), 606.1 (oligospermia), 606.8 (infertility due to extratesticular causes), and 606.9 (male infertility unspecified).

SOURCE: Healthcare Cost and Utilization Project Nationwide Inpatient Sample 1994, 1996, 1998, 2000.

Table 6. Ambulatory surgery visits for males with infertility listed as any diagnosis, 1994–1996 (merged and by year), count, rate[a] (95% CI), annualized rate[b], age-adjusted rate[c]

	1994–1996			
	Count	3-Year Rate	Annualized Rate	3-Year Age-Adjusted Rate
Total	55,411	61 (50–73)	20	61
Age				
18–24	*	*	*	
25–34	25,356	126 (88–165)	42	
35–44	17,078	83 (59–107)	28	
45+	7,463	20 (11–28)	6.7	
Region				
Midwest	15,250	72 (48–95)	24	72
Northeast	18,680	104 (64–143)	35	107
South	15,580	50 (35–66)	17	50
West	5,901	29 (16–42)	10	29
	1-Year Rate			
1994	20,788	24 (16–31)		
1995	15,858	17 (12–23)		
1996	18,765	20 (14–27)		

*Figure does not meet standard for reliability or precision.

[a]Rate per 100,000 is based on 1994, 1995, 1996 population estimates from Current Population (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US adult male civilian non-institutionalized population.

[b]Average annualized rate per year.

[c]Grouped years age-adjusted to the US Census-derived age distribution of the midpoint of years. Individual years age-adjusted to the US Census-derived age distribution of the year under analysis.

NOTE: Counts may not sum to total due to rounding.

SOURCE: National Survey of Ambulatory Surgery, 1994, 1995, 1996.

four-year observation period, they accounted for only 0.1% of all visits during that time period (Table 3)

TRENDS IN HEALTHCARE RESOURCE UTILIZATION

Inpatient and Emergency Room Care

Data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample, shown in Tables 4 and 5, indicate that during 1994, 1996, 1998, and 2000, there were 797 inpatient hospital stays for a primary diagnosis of male infertility among the US adult male civilian noninstitutional population. This represented an age-adjusted rate of 0.8 admissions per 100,000. The rate for men 18 to 34 years of age was 1.2 per 100,000, while the rate for men over 35 was 0.6 per 100,000. The admission rate per 100,000 was very similar among Caucasians and non-Caucasians (0.80 vs 0.70) but was higher among urban than among rural dwellers (749 of the 797 admissions were urban dwellers). It appears that 55% of the stays involved a diagnosis of varicocele (Table 5), which suggests that during the time of observation, varicocele repair was still sometimes undertaken in an inpatient setting.

Outpatient Care

According to data from the National Survey of Ambulatory Surgery, utilization of ambulatory surgical visits for male infertility is much higher, as shown in Table 6. This would be expected, given that surgical therapy for the management of male infertility is typically performed in an ambulatory setting. In 1994, 1995, and 1996, the cumulative rate of ambulatory surgery visits was 61 per 100,000 (a total of 55,411 visits nationally). Stratified by age, men 25 to 34 years of age appeared to have the highest utilization rate (126 per 100,000), followed by men 35 to 44 (83 per 100,0000), then men 45 and over (20 per 100,000), although overlapping confidence intervals suggest inadequate analytic power. Data were not sufficient to produce estimates for men aged 18 to 24. Men living in the Northeast had a rate of 104 per 100,000 ambulatory surgical visits associated with a diagnosis of male infertility, while those in the Midwest had 72 per 100,000 and those in the South had 50 per

100,000. Men living in the West had the lowest rate of ambulatory surgical visits, 29 per 100,000, which was significantly lower than men living in the Northeast or Midwest (104 and 72 per 100,000, respectively). The reason for this geographic variation is not clear but may relate to regional variations in insurance coverage for the treatment of infertility.

CHCPE data on ambulatory surgery visits also indicate a much higher utilization rate than was seen in the inpatient or ER setting, with the highest use being among individuals 25 to 34 years of age (Table 7).

CHCPE data on physician office visits for male infertility indicate that utilization is highest among men 25 to 34, followed by men 35 to 44 (Table 8). As was seen in the National Survey of Ambulatory Surgery data on ambulatory surgery visits, the utilization rate for physician office visits was far higher in the Northeast than in other parts of the country. It is noteworthy that according to National Ambulatory Medical Care Survey data, the rate of physician office visits for women with a primary diagnosis of infertility was also much higher in the Northeast than in the Midwest or West (Table 9). The concentration of infertility clinics in the Northeast may explain the higher rates of service utilization in that region.

Among 792,063 men seen in physician offices for the diagnosis of male infertility during 1992, 1994, 1996, 1998, and 2000, fully 53% (418,790 visits) were identified as having a diagnosis of varicocele (Table 10). This suggests that the incidence of varicocele among men being treated for infertility is higher than was previously estimated and highlights the importance of this clinical lesion among such patients.

Table 7. Ambulatory surgery visits for males with infertility having commercial health insurance, count, rate[a]

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
As Primary Diagnosis										
Total	140	39	175	32	279	32	325	32	253	29
Age										
18–24	17	*	20	*	32	29	42	33	37	35
25–34	61	70	89	66	112	54	139	63	100	54
35–44	52	51	45	29	91	36	91	33	80	34
45–54	9	*	18	*	34	17	39	17	23	*
55+	1	*	3	*	10	*	14	*	13	*
Region										
Midwest	85	39	92	30	123	29	155	32	145	31
Northeast	26	*	26	*	22	*	18	*	8	*
Southeast	21	*	44	28	119	34	132	32	89	25
West	8	*	13	*	15	*	20	*	11	*
As Any Diagnosis										
Total	146	41	187	34	295	33	347	35	275	31
Age										
18–24	19	*	20	*	33	30	44	34	37	35
25–34	63	72	90	66	123	60	144	65	109	59
35–44	54	53	51	33	92	37	101	37	88	37
45–54	9	*	21	*	37	19	43	19	28	*
55+	1	*	5	*	10	*	15	*	13	*
Region										
Midwest	89	41	101	32	130	31	165	34	153	33
Northeast	27	*	27	*	22	*	19	*	10	*
Southeast	21	*	46	30	125	36	142	35	100	28
West	9	*	13	*	18	*	21	*	12	*

*Figure does not meet standard for reliability or precision.
[a]Rate per 100,000 based on member months of enrollment in calendar years for males in the same demographic stratum.
SOURCE: Center for Health Care Policy and Evaluation, 1994, 1996, 1998, 2000, 2002.

Table 8. Physician office visits for males with infertility having commercial health insurance, count, rate[a]

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
As Primary Diagnosis										
Total	580	162	754	136	1,246	141	1,375	136.8	1,156	131
Age										
18–24	43	91	69	99	97	87	144	112	141	132
25–34	298	342	342	252	564	274	596	270	501	270
35–44	190	187	248	158	445	178	475	172	369	156
45–54	31	41	78	66	111	57	125	54	106	51
55+	18	*	17	*	29	*	35	25	39	31
Region										
Midwest	313	144	414	133	622	146	664	135	608	131
Northeast	163	315	125	223	178	245	134	226	76	202
Southeast	68	102	173	111	392	112.7	516	126.0	444	125
West	36	152	42	142	54	150	61	136	28	*
As Any Diagnosis										
Total	632	176	863	156	1,448	164	1,687	168	1,507	171
Age										
18–24	54	115	79	114	117	105	182	142	169	158
25–34	317	364	376	277	637	309	716	325	622	335
35–44	202	199	286	183	511	205	573	208	492	208
45–54	37	49	96	81	139	71	163	70	150	72
55+	22	*	26	*	44	34	53	37	74	55
Region										
Midwest	350	162	492	158	727	170	817	166	775	167
Northeast	170	329	130	232	191	263	145	245	100	266
Southeast	72	108	193	124	466	134	644	157	602	170
West	40	169	48	163	64	178	81	180	30	129

*Figure does not meet standard for reliability or precision.

[a]Rate per 100,000 based on member months of enrollment in calendar years for males in the same demographic stratum.

SOURCE: Center for Health Care Policy and Evaluation, 1994, 1996, 1998, 2000, 2002.

Table 9. Physician office visits by *females* with infertility listed as primary diagnosis, 1992–2000 (merged), count, rate[a] (95% CI), annualized rate[b], age-adjusted rate[c]

	1992–2000			
	Count	5-Year Rate	Annualized Rate	5-Year Age-Adjusted Rate
Total[d]	4,759,019	4,755 (3,848–5,663)	951	4,741
Age				
18–34	3,013,841	9,170 (7,033–11,308)	1,834	
35+	1,745,178	2,597 (1,741–3,452)	519	
Race/ethnicity				
White	3,919,766	5,227 (4,129–6,325)	1,045	5,455
Other	*		*	*
Region				
Northeast	2,237,450	11,022 (7,459–14,586)	2,204	11,500
Midwest	751,718	3,209 (2,035–4,383)	642	3,243
South	*	*	*	*
West	1,147,913	5,390 (3,600–7,180)	1,078	5,273
MSA				
MSA	4,094,638	5,345 (4,249–6,440)	1,069	5,215
Non-MSA	*	*	*	*

*Figure does not meet standard for reliability or precision.

MSA, metropolitan statistical area.

[a]Rate per 100,000 is based on 1992, 1994, 1996, 1998, 2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US adult female civilian non-institutionalized population.

[b]Average annualized rate per year.

[c]Age-adjusted to the US Census-derived age distribution of the midpoint of years.

[d]Persons of missing or unavailable race and ethnicity, and missing MSA are included in the total.

NOTE: Counts may not sum to total due to rounding.

SOURCE: National Ambulatory Medical Care Survey, 1992, 1994, 1996, 1998, 2000.

Table 10. Physician office visits by males with any diagnosis of infertility, by diagnosis code, count, percent[a]

		Male Infertility ICD-9 Code 606.X		Varicocele ICD-9 Code 456.4	
	Visits for male infertility	Count	Percent	Count	Percent
Total	792,063	407,569	51%	418,790	53%
Age					
18–34	482,679	*	*	*	*
35+	309,384	*	*	*	*
Race/ethnicity					
White	630,959	*	*	346,647	55%
Other	*	*	*	*	*
MSA					
MSA	629,331	383,038	61%	280,589	45%
Non-MSA	*	*	*	*	*

*Figure does not meet standard for reliability or precision.

MSA, metropolitan statistical area.

[a]Percent of weighted visits for any diagnosis of male infertility (within each demographic category) with diagnosis code.

NOTE: Counts were too low to report admissions for ICD-9 codes 606.0 (azoospermia), 606.1 (oligospermia), 606.8 (infertility due to extratesticular causes), and 606.9 (male infertility, unspecified).

SOURCE: National Ambulatory Medical Care Survey, 1992, 1994, 1996, 1998, 2000.

Varicocele

Varicocele was the most common diagnosis code among males undergoing ambulatory surgical procedures for the management of infertility (Tables 11 and 12). Indeed, according to data from the National Survey of Ambulatory Surgery, 67% of patients undergoing ambulatory surgery for the treatment of male infertility had a diagnosis of varicocele. The highest procedure rate appears to be among men 25 to 34 years of age.

According to CHCPE data, the most common diagnosis code among men seen for infertility in physician office visits was male infertility unspecified, followed by varicocele (Tables 13 and 14).

The Infertile VA Population

The Veterans Affairs (VA) Health System is a major healthcare provider for the male population of the United States. Data from the VA system for 1998 to 2003 show that the heavy users of care for male infertility in this population are once again young men between the ages of 25 and 34 (Table 15). Interestingly, the rate of infertility as a primary diagnosis rose steadily during the observation period among the three youngest age groups, which were also the most heavily represented in all three years. Another interesting finding in the VA data is that Caucasian males did not have the highest frequency of treatment for male infertility.

In civilian populations, Caucasians are typically the most frequent users of infertility resources. This is generally thought to be the result of socioeconomic factors related to the relatively high cost of such treatment, combined with the fact that fertility treatment is often not covered by insurance. In the VA system, where such factors presumably would not play as significant a role, the diagnosis of infertility was most frequent among Hispanics, followed by African Americans and then Caucasians. The VA database thus provides a unique perspective on the management of this disease state.

The VA data also examine the frequency of the diagnosis of male infertility by geographic location. While data on utilization of healthcare resources in the private sector consistently indicate that such resources are most heavily used in the Northeast and least heavily used in the West, this trend is not seen among VA patients. This supports the proposition that such trends may be influenced by geographic variations in health insurance coverage in the private sector.

Male Infertility and Artificial Reproductive Techniques

The treatment of male infertility has been dramatically affected by recent advances in assisted reproductive technology (ART). To assess the relationship between male infertility and the use of ART, we analyzed data from the Society for Assisted Reproductive Technology (SART). The SART database collects assisted reproductive technology procedure-related information from 399 member assisted reproductive medicine clinics. More than 95% of the assisted reproductive medicine clinics in the United States are represented in the SART database. Data are collected regarding age of both partners, the nature of the infertility problem identified in the couple, the technologies used in the infertility procedure, and the success rates of these procedures. SART and the Centers for Disease Control (CDC) jointly maintain a comprehensive database on the outcomes of ART in the United States, and this is the premier source of such information. All of the SART tables and figures pertain to couples for whom ART was utilized in the treatment of male infertility.

One statistic that stands out in the SART data on the use of IVF technologies in the treatment of male factor infertility is that well over 20,000 IVF procedures were performed for the management of this condition during the observation year. An IVF cycle typically costs from $10,000 to $20,000, so the contribution of IVF to the cost of treating male infertility is substantial. Such costs would not typically be captured, however, in analyses of expenditures made for this condition.

According to SART data, the age of the female partner (identified as the patient in this database) plays a very significant role in whether or not couples utilize ICSI in the IVF procedure. As shown in Table 16, the younger the partner, the more likely it is that ICSI would be incorporated in the IVF procedure. While the cost of applying ICSI technology to an IVF procedure varies from program to program, it typically increases the cost of the IVF cycle. Figure 2 details the presence of male factor infertility among couples using ICSI. Figure 3 compares couples with

Table 11. Ambulatory surgery visits for males with infertility due to scrotal varices having commercial health insurance, count, rate[a]

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
As Primary Diagnosis										
Total	89	17	111	14	167	14	198	14	167	14
Age										
18–24	15	*	17	*	27	*	36	28	34	32
25–34	44	51	65	48	77	37	82	37	76	41
35–44	28	*	22	*	50	20	51	18	39	17
45–54	2	*	5	*	10	*	24	*	14	*
55+	0	0	2	*	3	*	5	*	4	*
Region										
Midwest	56	18	47	11	65	11	90	13	89	14
Northeast	12	*	19	*	13	*	11	*	4	*
Southeast	14	*	33	15	79	17	81	15	65	14
West	7	*	12	*	10	*	16	*	9	*
As Any Diagnosis										
Total	95	18	119	15	176	14	217	16	186	16
Age										
18–24	17	*	17	*	28	*	38	30	34	32
25–34	46	53	65	48	84	41	86	39	84	45
35–44	30	30	25	*	50	20	60	22	45	19
45–54	2	*	8	*	11	*	27	*	19	*
55+	0	0	4	*	3	*	6	*	4	*
Region										
Midwest	60	19	54	12	69	12	100	15	96	15
Northeast	13	*	20	*	13	*	12	*	6	*
Southeast	14	*	33	15	81	17	88	16	74	16
West	8	*	12	*	13	*	17	*	10	*

*Figure does not meet standard for reliability or precision.

[a]Rate per 100,000 based on member months of enrollment in calendar years for males in the same demographic stratum.

SOURCE: Center for Health Care Policy and Evaluation, 1994, 1996, 1998, 2000, 2002.

Table 12. Ambulatory surgery visits by males with any diagnosis of infertility, by diagnosis code, count, percent[a]

		Male infertility ICD-9 Code 606.X		Varicocele ICD-9 Code 456.4	
	Visits for Male Infertility	Count	Percent	Count	Percent
Total	55,411	22,519	41%	37,070	67%
Age					
18–24	5,514	*	*	*	
25–34	25,356	9,885	39%	18,358	72%
35–44	17,078	7,630	45%	10,414	61%
45+	7,463			*	
Region					
Midwest	15,250	*	*	10,297	68%
Northeast	18,680	*	*	13,261	71%
South	15,580	7,213	46%	9,570	61%
West	5,901	*	*	*	

*Figure does not meet standard for reliability or precision.

[a]Percent of weighted visits for any diagnosis of male infertility (within each demographic category) with diagnosis code.

NOTE:Counts were too low to report admissions for ICD-9 codes 606.0 (azospermia), 606.1 (Oligospermia), 606.8 (Infertility due to extratesticular causes), and 606.9 (male infertility unspecified).

SOURCE: National Survey of Ambulatory Surgery, 1994, 1995, 1996.

Table 13. Physician office visits for males with unspecified infertility having commercial health insurance, count, rate[a]

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
As Primary Diagnosis										
Total	332	64	397	51	632	52	635	46	475	40
Age										
18–24	5	*	15	*	24	*	25	*	13	*
25–34	187	215	204	151	301	146	306	139	233	126
35–44	123	121	136	87	247	99	250	91	187	79
45–54	13	*	37	31	56	29	43	19	35	17
55+	4	*	5	*	4	*	11	*	7	*
Region										
Midwest	165	53	211	48	290	48	295	43	241	38
Northeast	125	169	91	115	141	141	104	130	52	104
Southeast	30	32	85	39	188	40	217	40	172	37
West	12	*	10	*	13	*	19	*	10	*
As Any Diagnosis										
Total	347	67	427	55	700	57	729	53	578	49
Age										
18–24	7	*	15	*	28	*	31	24	14	*
25–34	193	222	218	161	334	162	346	157	280	151
35–44	128	126	147	94	268	107	287	104	229	97
45–54	15	*	42	35	65	33	53	23	44	21
Region										
Midwest	176	56	232	52	328	55	339	50	286	45
Northeast	128	173	92	117	147	147	111	139	60	120
Southeast	31	33	92	43	208	44	255	47	221	48
West	12	*	11	*	17	*	24	*	11	*

*Figure does not meet standard for reliability or precision.

[a]Rate per 100,000 based on member months of enrollment in calendar yearsfor males in the same demographic stratum.

SOURCE: Center for Health Care Policy and Evaluation, 1994, 1996, 1998, 2000, 2002.

Table 14. Physician office visits for males with infertility due to scrotal varies having commercial health insurance, count, rate[a]

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
As Primary Diagnosis										
Total	202	39	274	35	426	35	559	41	507	43
Age										
18–24	34	72	51	74	63	56	109	85	127	119
25–34	87	100	102	75	184	89	206	93	186	100
35–44	56	55	80	51	119	48	158	57	115	49
45–54	11	*	31	26	40	21	65	28	52	25
55+	14	*	10	*	20	*	21	*	27	*
Region										
Midwest	124	40	154	35	226	38	270	40	278	44
Northeast	31	42	27	*	27	*	29	*	24	*
Southeast	29	*	69	32	142	30	228	42	190	41
West	18	*	24	*	31	57	32	48	15	*
As Any Diagnosis										
Total	237	46	342	44	542	44	752	55	717	61
Age										
18–24	42	89	60	87	78	70	139	108	153	143
25–34	99	114	119	88	215	104	276	125	244	132
35–44	63	62	101	64	160	64	207	75	185	78
45–54	15	*	43	36	55	28	93	40	83	40
55+	18	*	19	*	34	*	37	26	52	38
Region										
Midwest	150	48	203	46	283	47	365	54	380	60
Northeast	34	46	29	*	34	34	33	41	39	78
Southeast	32	34	81	38	189	40	308	57	282	61
West	21	*	29	*	36	66	46	68	16	*

*Figure does not meet standard for reliability or precision.

[a]Rate per 100,000 based on member months of enrollment in calendar years for males in the same demographic stratum.

SOURCE: Center for Health Care Policy and Evaluation, 1994, 1996, 1998, 2000, 2002.

Table 15. Male VA users with a diagnosis of infertility, 1998–2003, count, age-adjusted rate[a]

	1998		1999		2000		2001		2002		2003	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Total	2,033	62	2,105	60	2,206	59	2,183	53	2,310	52	2,318	49
Age-adjusted Total	2,160	58	2,144	58	2,206	59	2,111	57	2,157	58	2,109	57
Age												
< 25	32	110	47	159	43	147	54	184	63	215	68	230
25–34	262	158	280	169	322	194	341	206	368	222	381	230
35–44	354	97	367	100	412	113	445	122	506	138	485	132
45–54	553	67	606	74	619	76	589	72	563	69	547	67
55–64	341	55	327	52	311	50	310	50	312	50	289	46
65–74	400	41	319	33	324	34	239	25	216	22	213	22
75–84	203	30	181	27	160	23	124	18	125	18	120	18
85+	15	25	17	27	15	24	9	14	4	6	7	11
Race/ethnicity												
White	1,138	54	1,159	51	1,259	51	1,173	42	1,209	40	1,118	36
Black	485	103	463	96	428	88	416	85	403	82	393	82
Hispanic	109	120	96	102	111	115	106	106	101	98	95	94
Other	12	28	22	49	18	39	25	51	17	34	24	49
Unknown	289	50	365	61	390	66	463	70	580	73	688	66
Insurance Status												
No insurance/self-pay	1,589	66	1,661	66	1,691	69	1,614	65	1,675	66	1,607	64
Medicare	104	41	126	32	202	31	257	26	294	24	332	22
Medicaid	3	137	1	37	2	52	6	96	11	127	8	84
Private Insurance/HMO	329	53	308	53	291	51	284	48	307	47	349	50
Other Insurance	8	71	9	52	19	81	20	74	22	72	22	61
Unknown	0	0	0	0	1	115	2	105	1	35	0	0
Region												
Eastern	312	65	328	64	351	63	364	53	418	54	388	49
Central	276	48	306	49	327	51	290	40	363	41	399	38
Southern	907	73	803	60	893	62	938	58	1,002	55	1,024	53
Western	538	55	668	65	635	60	591	56	527	53	507	53

[a]Rate per 100,000 veterans using the VA system, age-adjusted to 2000.

SOURCE: Inpatient and Outpatient Files, VA Information Resource Center (VIReC), Veterans Affairs Health Services Research and Development Service Resource Center.

Table 16. Use of intracytoplasmic sperm injection (ICSI) in *females* undergoing *in vitro* fertilization, 1999, by age

	Count[a]	Percent
Total	22,426	
Age		
18–29	3,390	89.7%
30–34	7,763	86.7%
35–37	5,028	84.9%
38–40	3,785	83.4%
41–42	1,494	81.7%
42–66	966	80.6%

[a]7,596 were missing information on ICSI status.

SOURCE: Society for Assisted Reproductive Technology (SART)/ American Society of Reproductive Medicine (ASRM) database, 1999.

male factor infertility that used IVF with and without ICSI.

SART data confirm that the age of the female partner plays a critical role in the success of IVF in regard to both pregnancy and live birth rate. There is a direct relationship between the age of the female partner and the likelihood of achieving both pregnancy and live birth via IVF, with younger women being much more likely to become pregnant than their older counterparts (Tables 17). Since couples who are not successful during the first IVF cycle may choose to repeat the process, the cost of IVF is greater among those in whom the female partner is older. Additionally, when couples do not become pregnant during the first IVF cycle, subsequent cycles tend to be less successful.

The data in Table 18 suggest that the likelihood that a couple will become pregnant is also related to the ethnicity of the female partner. Unfortunately, these data were not controlled for age. If there is a correlation between the race and the age of the female partner, these results may be misleading.

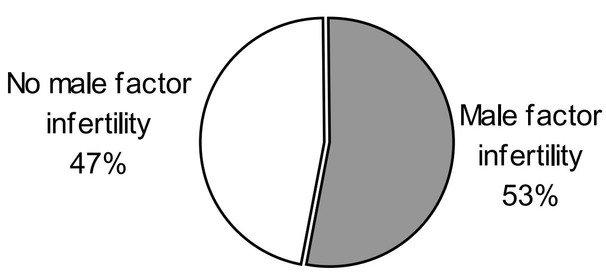

Figure 2. Presence or absence of male factor infertility diagnosis in 50,648 fresh non-donor cycles of ICSI, 2003.

SOURCE: Adapted from Center for Disease Control and Prevention, 2003 Assisted Reproductive Technology (ART) Report.

ECONOMIC IMPACT

Economic calculations based on data available for this analysis substantially underestimate actual costs, as location of care of infertility patients are atypical in the databases, and a substantial portion pay cash for services. In 2000, total expenditures for male infertility were approximately $17 million, a decrease of more than $2.5 million since 1994 (Table 19). This decrease can be attributed to reduced expenditures for ambulatory surgery. Costs for physician office visits remained constant from 1994 to 2000, but after inflation is accounted for, this represents a decrease in real expenditures. Additionally, IVF treatment based on 120,000 ART cycles at a cost of $15,000 per cycle puts the total cost at about $1.8 billion, (possibly dwarfing the rest of the costs in this section).

Individual-level expenditures for male infertility were estimated using risk-adjusted regression models controlling for age, work status, income, urban or rural residence, and health plan characteristics (Table 20). Among 18- to 64-year-old males with employer-provided insurance, average annual expenditures were $3,515 for those treated for male infertility, compared with $3,722 for similar men not treated for the condition. The apparent cost saving associated with male infertility is certainly an artifact and is likely a function of two factors: First, a selection effect may be operating in which men who seek treatment for infertility have generally better health than men of similar age not receiving treatment. Second, infertility costs often are not covered by health insurance, so the true costs resulting from an infertility diagnosis may be missing in claims data. We can only conclude that excess costs associated with diagnosis of male infertility appear to be modest with respect to

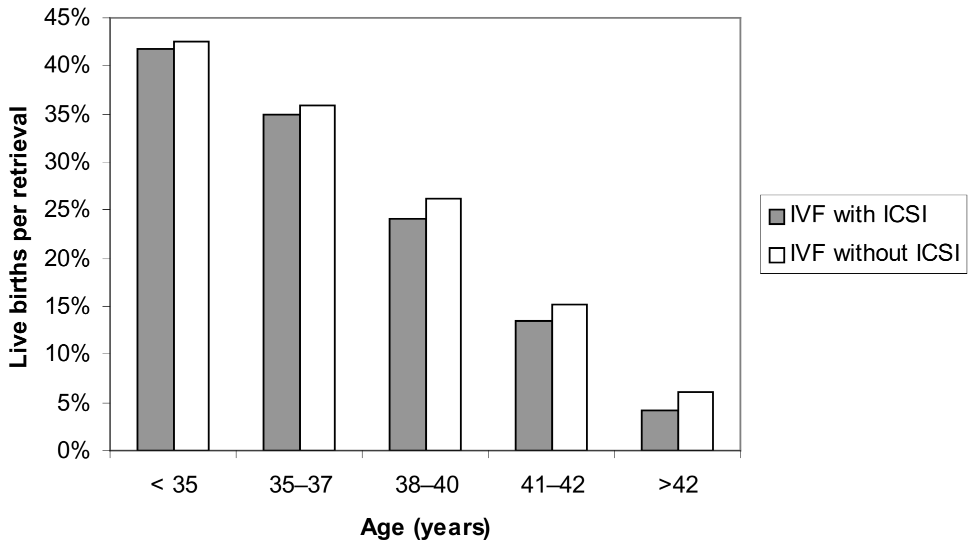

Figure 3. **Live births per retrieval for Assisted Reproductive Technology (ART) cycles using fresh non-donor eggs or embryos among couples diagnosed with male factor infertility who used IVF with or without ICSI, by woman's age[a] , 2003.**

[a]Cycles using donor sperm and cycles using gamete intra-fallopian transfer (GIFT) or zygote intra-fallopian transfer (ZIFT) are excluded. The comparison group of IVF without ICSI includes couples with all diagnoses except male factor infertility.

Source: Adapted from Center for Disease Control and Prevention, 2003 Assisted Reproductive Technology (ART) Report.

Table 17. Likelihood of outcomes in females undergoing *in vitro* fertilization, 1999, by age

	Pregnancy		Live Birth	
	N	Percent	N	Percent
Total	29,995		29,995	
Age				
18–29	4,350	37.5%	4,350	32.8%
30–34	10,298	33.9%	10,298	28.7%
35–37	6,659	30.1%	6,659	24.9%
38–40	5,151	24.9%	5,151	15.6%
41–42	2,084	19.5%	2,084	13.2%
43–66	1,453	22.0%	1,453	16.1%

Source: Society for Assisted Reproductive Technology (SART)/American Society of Reproductive Medicine (ASRM) database, 1999.

Table 18. Likelihood of a pregnancy in females when undergoing *in vitro* fertilization, 1999, by race/ethnicity

	Count	Percent
Total	29,995	
White, non-Hispanic	17,287	30.6%
Black, non-Hispanic	756	25.0%
Asian, non-Hispanic	1,041	27.2%
Hispanic	1,055	30.1%
Other, Unknown, and N. American Native	9,856	30.9%

Source: Society for Assisted Reproductive Technology (SART)/American Society of Reproductive Medicine (ASRM) database, 1999.

Table 19. Expenditures for infertility, by site of service (% of total)

Service Type	1994		1996		1998		2000	
Hospital Outpatient	---	0.0%	---	0.0%	---	0.0%	---	0.0%
Physician Office	$11,032,826	55.9%	$10,372,643	58.9%	$10,561,761	63.1%	$11,238,832	65.9%
Ambulatory Surgery	$8,707,207	44.1%	$7,226,463	41.1%	$6,168,275	36.9%	$5,807,572	34.1%
Emergency Room	---	0.0%	---	0.0%	---	0.0%	---	0.0%
Inpatient	---	0.0%	---	0.0%	---	0.0%	---	0.0%
TOTAL	$19,740,033		$17,599,105		$16,730,036		$17,046,404	

SOURCE: National Ambulatory and Medical Care Survey; National Hospital and Ambulatory Medical Care Survey; Healthcare Cost and Utilization Project; Medical Expenditure Panel Survey, 1994, 1996, 1998, 2000.

insurance but may pose a larger financial burden on patients themselves.

Approximately 8% of privately insured men in treatment for infertility missed some work related to their condition; the average work loss was 2.6 hours, the vast majority of which was for outpatient visits (Table 21). The proportion of men missing some work, as well as the number of hours missed, varied by age, with 14% of 18- to 29-year-olds missing an average of 5.0 hours. Overall, about 2.5 hours of work were missed for each outpatient visit for male infertility.

The relatively small economic impact of male infertility is a function of both low excess costs associated with the diagnosis and the low frequency with which treatment is sought for the condition; less than 0.5% of privately insured 18- to 64-year-old men had a claim for infertility. A majority of the costs related to infertility is likely to have been missed by these data, however, as patients typically pay a substantial amount of money out-of-pocket.

CONCLUSIONS

Approximately one of every seven couples who attempt to conceive will fail to do so within one year. Some form of reproductive pathology may be identified in the majority of couples, but at present, biases in the available surveys make it difficult to determine the proportions of male and female factors. It is likely, however, that approximately one-third of

Table 20. Estimated annual expenditures for privately insured male employees with and without a medical claim for infertility in 2002[a]

	Annual Expenditures (per person)					
	Males without Infertility (N=284,379)			Males with Infertility (N=952)		
	Medical	Rx Drugs	Total	Medical	Rx Drugs	Total
Total	$2,684	$1,038	$3,722	$2,487	$1,028	$3,515
Age						
18–34	$1,285	$654	$1,939	$2,411	$846	$3,257
35–44	$2,157	$880	$3,037	$1,746	$698	$2,444
45–54	$3,067	$1,217	$4,284	$3,154	$1,011	$4,165
55–64	$3,227	$1,138	$4,365	$2,411	$1,320	$3,731
Region						
Midwest	$2,599	$1,025	$3,624	$2,407	$1,019	$3,426
Northeast	$2,628	$1,122	$3,750	$2,434	$1,112	$3,546
South	$2,736	$974	$3,710	$2,534	$961	$3,495
West	$2,902	$1,067	$3,969	$2,688	$1,067	$3,755

Rx, Prescription.

[a]The sample consists of primary beneficiaries ages 18 to 64 having employer-provided insurance who were continuously enrolled in 2002. Estimated annual expenditures were derived from multivariate models that control for age, gender, work status (active/retired), median household income (based on zip code), urban/rural residence, medical and drug plan characteristics (managed care, deductible, co-insurance/co-payments) and binary indicators for 28 chronic disease conditions.

SOURCE: Ingenix, 2002.

Table 21. Average annual work loss of males treated for infertility, 1999 (95%CI)

	Number of Workers[a]	% Missing Work	Average Work Absence (hrs) Inpatient[b]	Outpatient[b]	Total
Total	278	8%	0.1 (0–0.3)	2.5 (1.1–3.9)	2.6 (1.2–4.1)
Age					
18–29	49	14%	0.7 (0–2)	4.4 (0–9.3)	5.0 (0–10)
30–39	159	7%	0	1.8 (0.4–3.3)	1.8 (0.4–3.3)
40–49	61	5%	0	3.1 (0–7.0)	3.1 (0–7.0)
50–64	9	0%	0	0	0
Region					
Midwest	93	9%	0	1.8 (0.4–3.3)	1.8 (0.4–3.3)
Northeast	16	6%	0	0.3 (0–0.8)	0.3 (0–0.8)
South	94	9%	0.3 (0–1)	2.9 (0.4–5.3)	3.2 (0.7–5.7)
West	44	7%	0	3.1 (0–8.2)	3.1 (0–8.2)
Unknown	31	3%	0	3.6 (0–11)	3.6 (0–11)

…data not available.

[a]Individuals with an inpatient or outpatient claim for infertility and for whom absence data were collected. Work loss based on reported absences contiguous to the admission or discharge dates of each hospitalization or the date of the outpatient visit.

[b]Inpatient and outpatient include absences that start or stop the day before or after a visit.

Source: Marketscan Health and Productivity Management, 1999.

couple infertility is due to the male alone, one-third to the female alone, and one-third to both partners. The available data indicate that men with reproductive dysfunction are either paying for their care themselves or are being treated simply as sperm donors for artificial reproductive techniques in the female. A report from the Bertarelli Foundation's second global conference on infertility in the third millennium put it well: "The current treatment of male infertility has become so dominated by the breakthrough technology of ICSI that a kind of nihilism has become widespread in the field." This cynical viewpoint was summed up as follows: "As long as a few motile sperm are present, no further review of the male is needed" (28). In view of the great expense of IVF and the sensible position of directly treating underlying disease in the infertile male, further systematic examination of the causes and treatment of male reproductive dysfunction is highly warranted. A quarter of a century ago, MacLeod noted that "the entire field of human male fertility (definitions, etiology and therapy) remains in a state of groping development that has gathered momentum only in recent years" (19). Oddly, the advent of a great technological breakthrough in reproductive therapy for the female, ICSI, caused that momentum to slip. It is time to regain it.

RECOMMENDATIONS

It is clear that much of the practice of male infertility is not identified in current large-scale databases. The following would further the diagnosis and treatment of male infertility and the understanding of its basis:

- A standardized list of male infertility diagnosis codes that identifies clinical and laboratory abnormalities (including semen analyses) independently.
- A large-scale, well-conducted survey of infertile couples, with the standardized list applied to the male to determine the gender distribution and epidemiology of infertility, as well as the related health resource expenditures.
- A large-scale study to correlate semen analysis parameters and the probability of conceiving, expressing the result in actual time to conceive.
- A new assay of male reproductive function with high sensitivity and specificity.

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