
Male Infertility

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Purpose: We assessed male infertility and its treatment in the United States by identifying trends in the use of health care resources and estimating the economic impact of such care.

Materials and Methods: The analytical methods used to generate these results were previously described.

Results: Inpatient hospitalizations for male infertility were relatively few with an overall rate of 0.9/100,000 population. Of these stays 55% were associated with inpatient management of varicocele and 749 of 797 occurred in a rural setting. Between 1994 and 1996 there were 55,411 ambulatory surgery visits with men 25 to 34 years old having the highest use rate of 61/100,000. Men living in the West had the lowest rate of ambulatory surgical visits, which was significantly lower than that for men living in the Northeast and Midwest (29/100,000 vs 104/100,000 and 72/100,000, respectively). The Veterans Affairs health system showed no geographic trend in infertility diagnosis and Hispanic men had the highest frequency of treatment for male infertility, followed by black and then white men. The National Survey for Ambulatory Surgery estimated that 67% of patients undergoing ambulatory surgery for male infertility had a diagnosis of varicocele. In 2000 total expenditures for treating primary male infertility were approximately \$17 million. However, adding the cost for assisted reproduction technology cycles placed total cost at about \$18 billion.

Conclusions: Infertile males generally seek infertility care outside of traditional reimbursement patterns. For this reason obtaining accurate data regarding the costs associated with male fertility care has proved to be challenging. Given the expense of in vitro fertilization and its attendant technologies, emphasis should be placed on addressing the underlying causes of male infertility. Further systematic examination of the demographics and management of male reproductive dysfunction is warranted.

Key Words: testis; infertility, male; health care costs; health services research; costs and cost analysis

Approximately 15% of all couples who attempt to conceive fail to do so within the first year.¹ A third of couple infertility cases can be attributed to male reproductive causes alone, a third can be attributed to female causes alone and a third can be attributed to male plus female causes.² Treatment for male infertility has benefited by the advent of female artificial reproductive techniques such as IVF but at substantial cost. The Bertarelli Foundation second global conference on infertility showed that “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.”³ We explored current trends in treating the infertile male by directly addressing underlying pathological conditions and by ARTs. We also estimated the economic impact of this disease.

MATERIALS AND METHODS

The analytical methods used to generate these results were described previously.

RESULTS

Trends in Health Care Use

Inpatient and ER care. Data from CHCPE and HCUP indicated that few patients with male fertility are treated in an inpatient or ER setting (data not shown). CHCPE describes the experience of more than 22 million member-years in an insured population, indicating that from 1994 to 2002 combined inpatient care for a primary diagnosis of male infertility was delivered on only 4 occasions and only 39 ER visits were made for a primary diagnosis of male infertility.

The HCUP National Inpatient Sample indicated that between 1994 and 2000 there were a total of 797 inpatient hospital stays for a primary diagnosis of male infertility in the adult male civilian noninstitutional population in the United States, representing a cumulative rate of 0.9 admissions per 100,000. The rate for men 18 to 34 years old was 1.2/100,000, while the rate for men older than 35 years was 0.6/100,000. The admission rate per 100,000 population was similar in white and nonwhite men (0.80 vs 0.70) but it was higher in urban than in rural dwellers

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TABLE 1. Ambulatory surgery visits for males with infertility as any diagnosis in 1994 to 1996

	Count	Rate (95% CI)	Av Annualized Rate/Yr	Age Adjusted Rate
Totals	55,411	61 (50-73)	20	61
Age:*				
25-34	25,356	126 (88-165)	42	
35-44	17,078	83 (59-107)	28	
45 or Older	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
Yr:				
1994	20,788	24 (16-31)	24	
1995	15,858	17 (12-23)	17	
1996	18,765	20 (14-27)	20	

Rate per 100,000 based on 1994, 1995 and 1996 population estimates from Current Population, CPS Utilities, Unicon Research Corp. for relevant demographic categories of adult male civilian noninstitutionalized population in the United States, grouped years age adjusted to the United States Census derived age distribution of the mid point of years and individual years age adjusted to the United States Census derived age distribution of the year under analysis (counts may not sum to total due to rounding) (source: National Survey of Ambulatory Surgery, 1994, 1995 and 1996).
* Values for ages 18 to 24 do not meet reliability or precision standard.

(749 of the 797 admissions were for urban dwellers). It appears that 55% of the stays involved a diagnosis of varicocele, which suggests that during the time of observation varicocele repair was still sometimes performed in an inpatient setting.

Outpatient care. According to NSAS data the use of ambulatory surgical visits for male infertility from 1994 to 1996 was much higher (table 1). This would be expected, given that surgical therapy for male infertility management is

typically performed in an ambulatory setting. From 1994 to 1996 the cumulative rate of ambulatory surgery visits was 61/100,000 population, representing a total of 55,411 visits nationally. When stratified by age, men 25 to 34 years old appeared to have the highest use rate, followed by men 35 to 44 and then men 45 years or older (126/100,000, 83/100,000 and 20/100,000, respectively). However, overlapping CIs suggested inadequate analytical power. Data were not sufficient to produce estimates for men 18 to 24 years old. Men living in the Northeast had a rate of 104/100,000 ambulatory surgical visits associated with a diagnosis of male infertility, while those in the Midwest had a rate of 72/100,000 and those in the South had a rate of 50/100,000. Men living in the West had the lowest rate of ambulatory surgical visits at 29/100,000. The reason for this geographic variation is not clear but it may relate to regional variations in insurance coverage for infertility treatment.

CHCPE data on ambulatory surgery visits also indicated a much higher use rate than that seen in the inpatient or ER setting with the highest use by among individuals 25 to 34 years old (data not shown).

CHCPE data on physician office visits for male infertility indicated that use was highest in men 25 to 34 years old, followed by men 35 to 44 years old (table 2). As seen in NSAS data on ambulatory surgery visits the use rate for physician outpatient visits was far higher in the Northeast than in other parts of the country. Of note, 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 (data not shown). The concentration of infertility clinics in the Northeast may explain the higher rates of service use in that region (fig. 1).

Varicocele was the most common diagnosis code in males seen in physician offices and undergoing ambulatory surgical

TABLE 2. Physician office visits for males with infertility who had commercial health insurance

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
	<i>Primary diagnosis</i>									
Totals	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 or Older	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	*
	<i>Any diagnosis</i>									
Totals	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 or Older	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	169.7
West	40	169	48	163	64	178	81	180	30	129

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 and 2002).
* Value does not meet reliability or precision standard.



FIG. 1. Sites of ART clinics in United States and Puerto Rico in 2003. Source: Centers for Disease Control and Prevention, 2003 ART Report.

procedures for male infertility management (tables 3 and 4). Indeed, according to NSAS 67% of patients undergoing ambulatory surgery for male infertility had a diagnosis of varicocele. The highest procedure rate appeared to be in men 25 to 34 years old. According to CHCPE data the most common diagnosis code in men seen for male infertility in physician outpatient visits was male infertility unspecified, followed by varicocele (tables 5 and 6).

VA Data on Infertility

The VA Health System is a major health care provider for the male population of the United States. Similar to the population at large, data from the VA system on 1998 to 2003 indicated that the primary users of care for male infertility in this population were young men between the ages of 25 and 34 years (table 7). Two discrepancies exist between data from the VA health system and from the private sector. Hispanic men had the highest frequency of treatment for male infertility, followed by black and then white men. VA data also examined the frequency of the diagnosis of male infertility by geographic location and showed no geographic trend, while private sector data consistently indicated that

TABLE 3. Physician office visits by males with any diagnosis of infertility by diagnosis code

	No. Male Infertility Visits	Male Infertility ICD-9 Code 606 Count (%)	Varicocele ICD-9 Code 456.4 Count (%)
Totals	792,063	407,569 (51)	418,790 (53)
Age:			
18-34	482,679	*	*
35 or Older	309,384	*	*
Race/ethnicity:			
White	630,959	*	346,647 (55)
Other	*	*	*
MSA	629,331	383,038 (61)	280,589 (45)

Percent of weighted visits for any diagnosis of male infertility each demographic category with diagnosis code with counts 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) and nonMSA values not meeting reliability or precision standard (source: National Ambulatory Medical Care Survey, 1992, 1994, 1996, 1998 and 2000).
* Value does not meet reliability or precision standard.

TABLE 4. Ambulatory surgery center visits by males with any diagnosis of infertility by diagnosis code

	No. Male Infertility Visits	Male Infertility ICD-9 Code 606 Count (%)	Varicocele ICD-9 Code 456.4 Count (%)
Totals	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 or Older	7,463	*	*
Region			
Northeast	18,680	*	13,261 (71)
Midwest	15,250	*	10,294 (68)
South	15,580	7,213 (46)	9,570 (61)
West	5,901	*	*

Percent of weighted visits for any diagnosis of male infertility in each demographic category with diagnosis code with counts 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 Survey of Ambulatory Surgery, 1994, 1995 and 1996).
* Value does not meet reliability or precision standard.

such resources were most heavily used in the Northeast and least heavily used in the West.

Male Infertility and ARTs

To assess the relationship between male infertility and the use of ARTs we analyzed SART data. Data on the age of the 2 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 was collected from 399 clinics, representing greater than 95% of assisted reproductive medicine clinics in the United States for 1 observational year. During this period well over 20,000 IVF procedures were performed for male factor infertility. Table 8 shows that younger partners were more likely to use ICSI with IVF procedures.

SART data confirmed a direct relationship between female partner age and the likelihood of achieving pregnancy and live birth via IVF with younger women more likely to become pregnant than their older counterparts (table 9). SART data suggested that the ethnicity of the female partner may affect IVF success but these data were not controlled for age (data not shown).

Economic Impact

In 2000 total expenditures for male infertility were approximately \$17 million, representing a decrease in annual expenditures of more than \$2.5 million since 1994 (table 10). This decrease could be attributable to reduced expenditures for ambulatory surgery. Costs for physician office visits remained constant from 1994 to 2000 but after inflation was accounted for this represented a decrease in real expenditures. Additionally, 1 IVF cycle typically costs \$10,000 to \$20,000, while applying ICSI technology increases the cost. Based on 120,000 ART cycles a cost of \$15,000 per cycle put the total cost at about \$1.8 billion, possibly dwarfing the rest of the cost in this section. Moreover, IVF technology is associated with an increased rate of multiple gestations. The markedly increased cost associated with multiple gestation pregnancies further adds to the cost of treating male factor infertility when ARTs are used. According to the 2003 Centers for Disease Control and Prevention report on ART 53%

TABLE 5. Physician office visits for males with unspecified infertility (ICD-9 code 606.9) who had commercial health insurance

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
	<i>Primary diagnosis</i>									
Totals	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 or Older	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	*
	<i>Any diagnosis</i>									
Totals	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	*

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 and 2002).

* Value does not meet reliability or precision standard.

of couples using IVF with ICSI were associated with a diagnosis of male factor infertility, although live birth rates for couples with male factor infertility were similar between the groups who did and did not undergo ICSI (fig. 2).

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 11). For 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 was certainly an artifact and likely a function of 2 factors. 1) A selection effect may have operated, in which

TABLE 6. Physician office visits for males with infertility due to scrotal varices (ICD-9 code 456.4) who had commercial health insurance

	1994		1996		1998		2000		2002	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
	<i>Primary diagnosis</i>									
Totals	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 or Older	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	*
	<i>Any diagnosis</i>									
Totals	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 or Older	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	*

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 and 2002).

* Value does not meet reliability or precision standard.

TABLE 7. Male VA users with infertility diagnosis in 1998 to 2003

	1998		1999		2000		2001		2002		2003	
	Count	Age Adjusted Rate	Count	Age Adjusted Rate	Count	Age Adjusted Rate	Count	Age Adjusted Rate	Count	Age Adjusted Rate	Count	Age Adjusted Rate
Totals	2,033	62	2,105	60	2,206	59	2,183	53	2,310	52	2,318	49
Age adjusted totals:	2,160	58	2,144	58	2,206	59	2,111	57	2,157	58	2,109	57
Younger than 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 or Older	15	25	17	27	15	24	9	14	4	6	7	11
Males	2,033	62	2,105	60	2,206	59	2,183	53	2,310	52	2,318	49
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 maintenance	3	137	1	37	2	52	6	96	11	127	8	84
Private insurance/health maintenance organization	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

Rate per 100,000 veterans using the VA system (source: Inpatient and Outpatient Files, VA Information Resource Center, VA Health Services Research and Development Service Resource Center).

men seeking treatment for infertility had generally better health than men of similar age not receiving treatment. 2) Infertility costs were often not covered by health insurance, so that the true costs resulting from an infertility diagnosis may have been missing in claims data. We can only conclude that excess costs associated with diagnoses of male infertility appear to be modest with respect to insurance but they may pose a larger financial burden on patients.

Approximately 8% of privately insured men on treatment for infertility missed some work related to the condition. The average work loss was 2.6 hours, of which the majority was for outpatient visits (table 12). 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 low excess costs associated with the diagnosis and the low frequency with which treatment was sought for the condition. Less than 0.5% of privately insured 18 to 64-year-old men had a claim for infertility. However, most costs related to infertility were likely to have been missed by these data since patients typically pay a substantial amount of money out of pocket.

DISCUSSION

Infertility is defined as failure to conceive within a certain period, typically 1 year. Clinicians commonly cite a 15% rate of couple infertility at 1 year and this rate is likely not far off the mark. Simmons referred to the 15% rate in 1956 but cited "information from reliable sources" without specific evidence.⁴ MacLeod referred to a 15% rate in 1971, candidly

TABLE 8. ICSI in females undergoing in vitro fertilization in 1999 by age

	Count (%)*
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)

* Missing ICSI status information for 7,596 females (source: SART/American Society of Reproductive Medicine database, 1999).

TABLE 9. Likelihood of outcomes in females undergoing in vitro fertilization in 1999 by age

	No. Pregnancy (%)	No. Live Birth (%)
Totals	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)
42-66	1,453 (22.0)	1,453 (16.1)

Source: SART/American Society of Reproductive Medicine database, 1999.

TABLE 10. Infertility expenditures by service site

	\$ Expenditure (%)
1994:	
Hospital outpt	— (0.0)
Physician office	11,032,826 (55.9)
Ambulatory surgery	8,707,207 (44.1)
ER	— (0.0)
Inpt	— (0.0)
Total	19,740,033
1996:	
Hospital outpt	— (0.0)
Physician office	10,372,643 (58.9)
Ambulatory surgery	7,226,463 (41.1)
ER	— (0.0)
Inpt	— (0.0)
Total	17,599,105
1998:	
Hospital outpt	— (0.0)
Physician office	10,561,761 (63.1)
Ambulatory surgery	6,168,275 (36.9)
ER	— (0.0)
Inpt	— (0.0)
Total	16,730,036
2000:	
Hospital outpt	— (0.0)
Physician office	11,238,832 (65.9)
Ambulatory surgery	5,807,572 (34.1)
ER	— (0.0)
Inpt	— (0.0)
Total	17,046,404

Source: National Ambulatory and Medical Care Survey, National Hospital and Ambulatory Medical Care Survey, HCUP and Medical Expenditure Panel Survey, 1994, 1996, 1998, and 2000.

attributing the value to “rather hackneyed but probably reliable statistics in the United States and in all countries where reliable records are kept.” In this landmark study 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.⁵ In 1 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. 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.⁶ Page, who was 1 of the first to attempt to determine the prevalence and incidence of infertility in a population, calculated that a study of 3,500 individuals would be sufficient to decrease the CIs to acceptable levels.⁷ In 1991 WHO published tables based on data that were then available.¹ Although the incidence of infertility varied somewhat by location, as MacLeod noted 20 years earlier,⁵ 15% was a remarkably reasonable assessment.¹

In the 1990s investigators reported fertility rates from localized regions around the world. Gunnell et al followed the recommendations of Page⁷ and sent questionnaires to more than 3,000 British women.⁸ When failure to conceive after 1 year was used as the definition of infertility, the overall incidence was 16.1% (95% CI 14.6 to 17.6), which was again remarkably similar to the often cited 15% rate. 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. Philippov et al reported a 16.7% overall incidence of infertility for 2,000 married women 18 to 45

years old in Tomsk, Western Siberia,⁹ which was interestingly close to the rate reported in Somerset. Given the diagnoses available in the study, the gender distribution was 38.7% for the 2 partners, 52.7% for the female partner only, 6.4% for the male partner only and 2.2% undetermined. However, the study was hampered by a small sample of 168 men and limited male diagnoses. Interestingly 45.7% of the males studied had abnormal semen analyses with a 9.1% rate of azoospermia.⁹ Ikechebelun et al reported gender specific infertility rates in 314 Nigerian couples, defining male infertility based on abnormal semen analysis alone.¹⁰ In contrast to the results reported by Philippov et al,⁹ a positive male factor alone was found in 42.4% of the couples in the Nigerian cohort, while in 25.8% the female alone appeared to be responsible.¹⁰ 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%. In almost a mirror image of these findings Bayasgalan et al reported data on 430 infertile couples in Mongolia.¹¹ A female factor alone was identified in 45.8% of the couples, while a male factor alone was found in 25.6%. In 9.8% of the couples no demonstrable cause was found in either partner and in 18.8% the 2 partners appeared to be responsible. Given the similarity in the overall incidence of couple infertility, the variability in these results may have been more likely due to study methodology and sampling biases rather than to local geographic factors. It is tempting to speculate that, if all biases were accounted for, about a third of infertility would be due to the female alone, a third would be due to the male alone and a third would be due to the 2 partners.²

However, epidemiological statements regarding male reproductive dysfunction present formidable challenges. While male patient fertility status may be the primary subject of analysis, a positive fertility outcome is manifested by another individual, that is the mother (who may have fertility related issues) giving birth to a child. If a good assay were available for only 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 in the set of couples that failed to conceive within 1 year. To our knowledge such an assay does not currently exist.

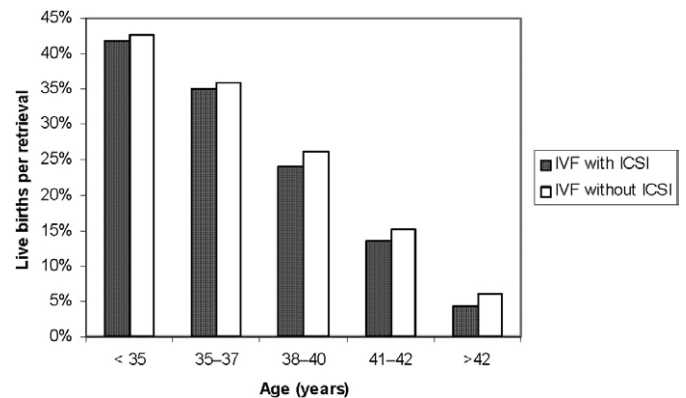


FIG. 2. Live births per retrieval for ART cycles using fresh nondonor eggs or embryos in couples diagnosed with male factor fertility who used IVC with vs without ICSI by female age in 2003, excluding cycles using donor sperm and those using gamete or zygote intrafallopian transfer. IVF comparison group included couples with all diagnoses except male factor infertility. Source: Centers for Disease Control and Prevention, 2003 ART Report.

TABLE 11. *Estimated annual expenditures for privately insured male employees with and without infertility medical claim in 2002*

	\$ Annual Expenditures/Pt Without Infertility (284,379 men)			\$ Annual Expenditures/Pt With Infertility (952 men)		
	Medical	Prescription Drugs	Totals	Medical	Prescription Drugs	Totals
All	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

Primary beneficiaries 18 to 64 years old with employer provided insurance who were continuously enrolled in 2002, estimated annual expenditures derived from multivariate models controlled 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 and co-insurance/co-payments) and binary indicators for 28 chronic disease conditions (source: Ingenix, 2002).

Raw data from the seminal 1951 report by MacLeod indicate that the ROC curve area for semen density to predict infertility is 0.59 and that for motility is 0.50,¹² literally no better than flipping a coin. In the large study by Guzick et al 50 years later the ROC area for semen density was 0.60, that for motility was 0.59 and that for morphology was 0.66,¹³ of which none inspires confidence in the predictive ability of bulk semen analysis. In fact, using the findings from a classification and regression tree analysis these investigators suggested using 2 thresholds for each bulk seminal parameter to counsel male patients about their reproductive potential.^{12,13}

Causes of male infertility may be simply divided into surgical or medical in nature. Medical diagnoses include immunological conditions such as antisperm antibodies, infectious diseases that may result in surgical diagnoses if anatomical obstruction ensues, endocrinopathy, gonadotoxin exposure and systemic illness, eg cancer. Surgical diagnoses include ductal obstruction (ductal refers to the entire reproductive anatomical tract), congenital anatomic anomalies, varicocele and erectile dysfunction. Certain diagnoses overlap into the 2 categories, such as cryptorchidism, in which the undescended testis exerts an as yet incom-

pletely understood toxic effect on the contralateral descended testis, or genetic conditions, such as hermaphroditism or congenital absence of the vas deferens. Other diagnoses fail to be properly categorized by these 2 distinctions, such as spermatogenic dysfunctions (hypospermatogenesis, maturation arrest and Sertoli-cell-only syndrome) and specific sperm anomalies (necrospemia). 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. Currently these 2 outlying categories may be considered medical. Interestingly between 1978 and 1997 more potential diagnoses became available but the proportion of men with idiopathic causes of infertility remained similar at approximately 25% in 1978 and 23% in 1997.^{14,15}

While not as dramatic as the decrease in fecundability with increasing maternal age, according to recent evidence male fertility also appears to decrease with age due to decreased sperm function and accumulating genomic damage. Other risk factors for male reproductive dysfunction are gonadotoxins such as chemotherapeutic agents, radiation exposure and various pharmaceutical agents that act as direct spermatotoxins or through a steroidal pathway. Common drugs known to impair male fertility include cimetidine, sulfasalazine, nitrofurantoin, ethanol, cannabis and androgenic steroids. 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 partner.¹⁵⁻¹⁸

Treatment for male infertility is multimodal because it involves targeted therapy to specific medical and surgical diagnoses, empirical pharmacological agents intended to improve spermatogenesis and ARTs used to bypass reproductive barriers in the female genital tract. Underlying male pathology may be directly addressed therapeutically by the urologist. However, if sufficient motile sperm are available (generally numbering in the millions), they may usually be placed directly through the cervix into the uterus by the gynecologist. If fewer sperm are available, IVF may be used. In a substantial technological leap Palermo et al described a technique referred to as ICSI, in which a single sperm is injected into an ovum.¹⁹ ICSI is required when sperm are surgically extracted directly from the testis because the

TABLE 12. *Annual work loss of males treated for infertility in 1999*

	No. Workers (% missing work)	Av Hrs Work Absence (95% CI)		
		Inpt	Outpt	Totals
Totals	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 (0-10.1)
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:				
Northeast	16 (6)	0	0.3 (0-0.8)	0.3 (0-0.8)
North Central	93 (9)	0	1.8 (0.4-3.3)	1.8 (0.4-3.3)
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 (0-11.0)	3.6 (0-11.0)

Individuals with an inpatient or outpatient claim for infertility and for whom absence data were collected with work loss based on reported absences contiguous to the admission or discharge dates of each hospitalization, or the date of the outpatient visit, and inpatient and outpatient data including absences that started or stopped the day before or after a visit (source: Marketscan Health and Productivity Management, 1999).

sperm are immature. According to SART data the age of the female partner has a significant role in whether couples use ICSI in the IVF procedure. The younger the partner, the more likely it is that ICSI would be incorporated into the IVF procedure. While the cost of applying ICSI technology into an IVF procedure varies among programs, it typically increases the cost of the IVF cycle. Also, since couples who are not successful during the first IVF cycle may choose to repeat the process, the cost of IVF would likely be greater for those in whom the female partner is older. Unfortunately when couples do not achieve pregnancy during the first IVF cycle, subsequent cycles tend to be less successful.

In civilian populations white individuals are typically the most frequent users of infertility resources. In the VA system the diagnosis of infertility in treated patients was most frequent in Hispanic individuals, followed by black and then white individuals. Thus, the VA database provides a unique perspective on the management of this disease state and it supports the proposition that such trends may be influenced by geographic variations in health insurance coverage in the private sector.

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 managing male infertility appears to be relatively small compared with health care 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, it may be underrepresented in databases that use information provided by health insurance entities. Given these caveats, male infertility appears to represent a relatively small percent of ambulatory health care 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 male infertility during a 4-year observation period, they accounted for only 0.1% of all visits during that time.

It is clear that much of the practice of male infertility is not identified in current large-scale databases. Certain suggestions would further the diagnosis and treatment of male infertility, and the understanding of its basis, including 1) a standardized list of male infertility diagnosis codes that identifies clinical and laboratory abnormalities (including semen analyses) independently, 2) a large-scale, well performed 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, 3) a large-scale study to correlate semen analysis parameters and the probability of conceiving, expressing the result in actual time to conceive and 4) an assay of male reproductive function with a high ROC area.

CONCLUSIONS

Approximately 1 of every 6 couples who attempt to conceive fails to do so within 1 year. Some form of reproductive pathology may be identified in the majority of couples but currently biases in the available surveys make it difficult to determine the proportion of male and female factors. How-

ever, it is likely that approximately a third of couple infertility is due to the male alone, a third is due to the female alone and a third is due to the 2 partners. Available data indicate that men with reproductive dysfunction are paying for their care or functioning as sperm donors for ART in females. In view of the great expense of IVF and the sensible position of directly treating underlying disease in infertile males further systematic examination of the causes of and treatment for male reproductive dysfunction is highly warranted.

Abbreviations and Acronyms

ART	=	assisted reproductive technology
CHCPE	=	Center for Health Care Policy and Evaluation
ER	=	emergency room
HCUP	=	Health Care Cost and Utilization Project
ICD-9	=	International Classification of Diseases, 9th revision
ICSI	=	intracytoplasmic sperm injection
IVF	=	in vitro fertilization
MSA	=	metropolitan statistical region
NSAS	=	National Survey of Ambulatory Surgery
SART	=	Society for ART
VA	=	Veterans Affairs

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