

# Distribution of Causes of Infertility in Patients Attending Primary Fertility Clinics in Israel

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**ABSTRACT:** **Background:** Infertility is one of the most prevalent health disorders in young adults.

**Objectives:** To study the distribution of causes of infertility in couples referred to primary infertility clinics in Israel.

**Methods:** Data for a 9 year period were derived from two clinics of major women's hospitals run by the country's largest health insurance fund. All patients were treated by one physician. Laparoscopy was not performed to rule out endometriosis.

**Results:** Of the 2515 couples identified, 1991 (79.2%) had a definitive diagnosis following complete workup (including hysterosalpingography). Mean age was  $29.6 \pm 6.0$  years; mean duration of infertility was  $1.7 \pm 1.8$  years. Primary infertility accounted for 65% of cases. Causes of infertility were male factor (45%), oligo-ovulation disorders (37%), and tubal damage (18%). Infertility factors were identified in the woman alone in 30.6% of cases and the man alone in 29.2%. Two combined infertility factors were found in 18% of patients, and three combined factors in 0.5%. The rate of unexplained infertility (which probably includes non-tubal endometriosis) was 20.7%.

**Conclusions:** As male factor accounts for almost half of all cases of infertility in couples, sperm analysis is mandatory before any treatment.

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**KEY WORDS:** infertility diagnosis, epidemiological survey, sperm analysis

Infertility is one of the most prevalent health disorders in young adults. Diagnostic assessment of infertility is indicated when pregnancy has not occurred within one year of regular unprotected intercourse, by which time 85–90% of couples attempting conception should be successful [1]. Earlier assessment is needed in women with a history of oligomenorrhea/amenorrhea or suspected pelvic pathology, and in cases with suspected male factor infertility. Infertility has three main causes: anovulation, mechanical factor, and male factor. Some patients have a combination of these conditions;

in others, the results of infertility workup are normal, leading to a diagnosis of unexplained infertility.

The distribution of the causes of infertility is population-dependent [2]. Several epidemiological reports have already been published profiling the infertile population in different countries. In the present study, we collected data from two primary infertility clinics run by the largest nationwide health fund in order to examine the distribution of causes of infertility in Israel.

## PATIENTS AND METHODS

The study population consisted of 2515 couples who attended the fertility clinics of two centrally located women's health centers in Israel between January 1999 and December 2007. The study was approved by the ethics committee of Clalit Health Services, the largest health management organization in the country, which runs both centers. All couples were admitted and treated by the same gynecologist (J.F.), and all underwent the same routine management protocol, based on the recommendations of the ESHRE Capri Workshop Group [3].

According to the clinic's routine management protocol, at the first visit, couples complete a referral status form which covers the basic medical history of both partners. Data include age, chronic illnesses and/or prior hospitalizations, regular use of medications, duration of child wish (i.e., time from onset of unprotected intercourse to first infertility consultation), smoking habits, previous general or pelvic surgery; and for women, menstrual regularity, dysmenorrhea, dyspareunia, and history of pelvic inflammatory disease.

Thereafter, couples are referred for infertility investigation, starting with a hormonal analysis in women (follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone, estradiol, and DHEAS) on day 3–5 of either a spontaneous or induced menstrual period, and a semen analysis in men. This is followed directly by hysterosalpingography when the results indicate regular menstrual cycles, normal hormone levels, and a sperm count that is either normal or suitable for intrauterine insemination ( $> 5 \times 10^6$  total motile count). In couples found to have anovula-

tory infertility (defined below), HSG is deferred until a trial of clomiphene citrate is completed, and it is then done before or within the first two ovulation-induction treatments using gonadotropin. HSG is not performed in cases of known bilateral tubal factor or severe male factor necessitating in vitro fertilization, or when the laparoscopy results indicate pelvic factor or severe endometriosis.

#### CLASSIFICATION OF INFERTILITY CAUSES

The causes of infertility were defined according to the following criteria:

- *Oligo/anovulatory infertility* was defined as a menstrual cycle length of more than 35 days. Within this category, polycystic ovary syndrome was defined as the presence of at least two of the Rotterdam criteria [4]: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound. Other factors associated with oligo-ovulation or anovulation were investigated as part of the day 3–5 hormonal profile: 21-hydroxylase deficiency, by the basal morning 17-hydroxyprogesterone level; thyroid dysfunction, by level of TSH; hypogonadotropic and hypergonadotropic hypogonadism, by level of (low) E<sub>2</sub> and by FSH concentration (low or high, respectively) [5]; and hyperprolactinemia.

HSG = hysterosalpingography  
TSH = thyroid-stimulating hormone  
E<sub>2</sub> = estradiol  
FSH = follicle-stimulating hormone

**Table 1.** Distribution of patients according to cause of infertility

Overall causes of infertility (isolated or combined)	No. of couples*	% of diagnosis*	Subdivided	No. of couples	%
Oligo-ovulation	737	37	Isolated	455	22.8
Male factor	908	45.6	Isolated teratozoospermia	208	10.4
			Oligoteratoasthenospermia	375	18.8
Tubal factor	276	13.8	Unilateral	92	4.6
			Bilateral	64	3.2
Combined			Oligo-ovulation and male factor or teratozoospermia	239	12.0
			Oligo-ovulation and tubal (unilateral and bilateral factor)	34	1.7
			Tubal and male factors	77	3.9
			Oligo-ovulation, male factor and tubal factor	9	0.5
Unexplained	414	20.8		414	20.8
Others	25	1.3	Sexual, religious	25	1.3
Total	1992			1992	

\*One or more diagnoses

- *Male factor infertility* was defined by routine parameters: low sperm count of  $< 20 \times 10^6$  sperm cells/ml (oligozoospermia);  $< 50\%$  sperm motility (asthenozoospermia); and/or abnormal morphology of  $< 40\%$  according to World Health Organization criteria [6], or  $14\%$  according to the criteria of Kruger et al. [7] (teratozoospermia). The diagnosis was based on abnormal findings on two tests performed at least 4 weeks apart.
- *Mechanical factor infertility* was defined according to the findings on HSG. In all cases, the HSG results were analyzed first by the physician who performed the procedure and then by the treating gynecologist (J.F. in all cases). In the event of a discrepancy between the interpretations, the X-ray was reviewed by a third gynecologist for a final diagnosis. Uterine pathology was categorized as an irregular shaped space-occupying lesion(s), or a malformation indicating a congenital anomaly (arcuate, septated, uni-cornuate or bi-cornuate uterus). Tubal pathology was categorized as unilateral or bilateral and further subdivided into proximal occlusion, mid-distal occlusion, or hydrosalpinges.
- *Unexplained infertility* was diagnosed when all the above factors were within normal limits.

## RESULTS

Of the 2515 couples referred to the infertility clinics during the period of the study, 1992 (79.2%) had a definitive diagnosis after complete workup, and these formed our study group. The mean age of the women was  $29.6 \pm 6.0$  years and the mean duration of infertility  $1.7 \pm 1.8$  years. Primary infertility accounted for 65% of cases. Table 1 presents the distributions of the causes of infertility: male factor was the most common cause (45%), followed by oligo-ovulation disorders (37%) and tubal obstruction (mechanical factor) (18%). Infertility factors were identified only in the woman in 30.6% of couples and only in the man in 29.2%. A combination of two factors was found in 18% of patients and of three factors in 0.5%. The rate of unexplained infertility was 20.7%.

## DISCUSSION

This is the largest detailed report on the distribution of causes of infertility in primary infertility centers in Israel. The study presents results on 1991 couples who completed our full workup. The most common cause of infertility was male factor (45%), followed by oligo-ovulation disorders (37%) and tubal damage (18%). The woman alone was responsible for the couple's infertility in 30.6% of cases and the man alone in 29.2%. Two combined infertility factors were found in 18% of patients, and three in 0.5%. The rate of unexplained infertility (which probably includes endometriosis with no tubal or pelvic damage on HSG) was 20.7%.

**Table 2.** Comparison of studies on distribution of cause of infertility conducted in primary infertility clinics in different countries

Author	Country	Date	Anovulation	Male	Tubal	Unexplained	Combined
Present study	Israel	2010	37%	45%	18%	20.7%	18%
Elussein et al. [25]	Sudan	2008	29.7%	36.2%	19.5%	13.0%	—
Chiamchanya & Su-angkawatin [11]	Thailand	2008	20.8%	74%	21.5%	4.7%	55.6%
Bayasgalan et al. [10]	Mongolia	2004	—	25.6%	32.8%	9.8%	18.8%
Stewart-Smythe & van Iddekinge [12]	South Africa	2003	27%	82%	81.5%	—	—
Philippov et al. [13]	Siberia	1998	17.3%	45.1%	31.6%	2.2%	38.7%
Zargar et al. [14]	India	1997	21.6%	27.6%	11.6%	14.8%	14.8%
Thonneau & Spira [15]	France	1992	32%	57%	26%	—	39%
Haxton & Black [24]	Scotland	1987	31%	17%	18%	32%	—
Hull et al. [23]	UK	1985	21%	24%	14%	28%	—
Dor et al. [16]	Israel	1977	31.5%	28%	16.3%	17.6%	—

Table 2 presents the results of previous studies on the distribution of causes of infertility in different populations. As in the present survey, male factor was the most common diagnosis in most of the studies conducted in primary fertility care centers [2,8]. It was the single diagnosis in 17–57% of patients, and it was combined with other diagnoses in 14–55% [8-15]. By contrast, an early study from Israel on causes of infertility reported a considerably lower rate of male factor (28%) than we found [16]. Some studies, though not all, have noted a decline in sperm quality over the last few decades in the general population [17,18]. Most attributed the decline to factors related to environmental exposure [19]. However, ours is the first study to report a nearly twofold increase in the incidence of male factor in similar infertile populations attending primary infertility centers evaluated 30 years apart in the same country.

Ovulation disorders are the second most common cause of infertility in most surveys, with rates ranging between 21% and 50% [8,20,21]. In contrast to the rising incidence of male factor infertility, the incidence of ovulation disorders seems to have remained fairly constant over the last 30 years in different populations [Table 2]. In the 1977 study from Israel, Dor et al. [16] reported ovulation disturbances in 33.4% of 655 infertile couples, compared to 37% in the present study.

Tubal factor has the widest range of incidence among the causes of infertility, between 11% and 88%. Lunenfeld and Insler [2] summarized the diagnostic categories established in 6549 infertile couples managed by different investigators on five continents. They found that the incidence of tubal factor ranged from 11.0% to 76.7%. This variance was mostly associated with geography and developmental status of the country in which the survey was performed. In our population, in Israel, the incidence of tubal factor was a relatively low 18%, similar to the 16% reported by Dor et al. [16] three decades ago.

The reported prevalence of combined causes of infertility is as high as 30% [9,22]. In the present study, the incidence was 18%. Our rate of unexplained infertility was 20.7%. Researchers estimated that after proper and comprehensive investigation, no cause will be identified for infertility in 10% to 20% of infertile couples [22]. Nevertheless, at least part of the difference in rates among studies is probably a consequence of the variable diagnostic protocols used and the composition of the specific populations. In the study by Lunenfeld and Insler [2] of 6549 infertile couples, the incidence of unexplained infertility ranged from 3.5% to 22%. They found that the protocols applied in the different studies varied mainly in the investigation of mechanical factor, and specifically in the decision to perform or not to perform laparoscopy. Indeed, in our clinics, which use a treatment-oriented approach, laparoscopy is not routinely performed.

Another aspect that might have skewed the distribution results in our survey was the exclusion of couples with a partial diagnosis, who accounted for 20.8% of the whole population attending our clinics during the period of the study. Partial results were also reported in other surveys of infertility etiology, at rates of 15–50% [13].

In summary, male factor accounts for almost half of all causes of infertility in couples. Therefore, sperm analysis is mandatory prior to any infertility treatment. Male factor seems to have become more prevalent in the last 30 years, taking the lead over ovulation disorders.

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