Economic Evaluation of Infertility Treatment for Tubal Disease

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Purpose: The number of published studies comparing cost-effectiveness of tubal surgery and IVF treatment is limited, in part because of the difficulties of conducting randomized trials, given that IVF is now a clinically accepted treatment and the decision to offer surgery or IVF is often dictated by the severity of the tubal disease and by the availability of the methods. The aim of this study was to compare the costs of our policy of offering tubal surgery to patients with mild or moderate tubal disease with the cost of offering IVF to these and severe tubal disease.

Methods: In this retrospective cohort study patients with tubal pathology as the sole reason for their infertility were included: 61 patients in the tubal surgery group and 464 patients in the IVF group. The delivery rates and costs per delivery were compared.

Results: Delivery rates were 28% in the tubal surgery group within 2 years of follow-up and 52% in the IVF group that involved up to three cycles of treatment. This economic evaluation demonstrated only small differences in the average cost when considering the cost per delivery.

Conclusions: With a policy involving strict selection of patients, tubal surgery will continue to have a role in the treatment of infertility.

KEY WORDS: Cost; infertility; in vitro fertilization; tubal surgery.

INTRODUCTION

Assessments of the costs of conducting economic evaluations of different treatments have become increasingly important for financial decision makers and the medical profession alike. When politicians and health care providers impose budget limitations, it becomes a challenge for clinicians to maximize the benefit for their patients within the allocated resources. The assessment of benefit for the individual patient often is a choice between two or more

treatments and will involve not only medical decisions but also subjective valuation depending on the views of the physician or other persons involved in choosing the treatment (1). Access to treatment is another important consideration when the clinician decides which treatment option to recommend for the patient (2).

The basis of cost analysis is to compare both costs and outcomes for different treatments (3). In analysis of infertility treatment the outcome is commonly presented as clinical pregnancy or live birth. Although the outcomes are relatively more easily measured with infertility treatments than with many other health care procedures, it may still be difficult to make comparisons among various studies of infertility. Factors that can differ among clinics and may have an effect on the overall analysis include variations in the prevalence of certain infertility diagnoses, age of the patients and duration of infertility, policies for limitation

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of access to programs, and success rates. Differences in health care funding policies among countries can also make international comparisons of studies problematic. For example, cost estimations for in vitro fertilization (IVF) in the United States are often higher than those countries in Europe with publicly funded health care systems (4).

In the early years following the introduction of IVF into common practice, studies were undertaken to evaluate the cost-effectiveness of this new treatment with tubal surgery as the standard therapeutic option for women with tubal infertility (5,6). In a Norwegian study (5) it was concluded that the cost per live birth was considerably lower with IVF than with tubal surgery, while in the study from Haan and Van Steen (6) tubal surgery and IVF for patients with tubal pathology were equally cost-effective. Since these studies were performed, many aspects of infertility treatment have changed considerably. The success rate of IVF treatment has improved and several new indications can now be treated successfully. For patients with tubal pathology, the improved success rate has resulted in a shift in treatment from surgery to IVF. But at the same time, in many countries, a discrepancy still exists in the payment of costs, with full coverage being provided for tubal surgery and lower or no coverage for IVF treatment. Policies such as these may, from a financial viewpoint, lead physicians and patients to choose surgical treatment over IVF without regard to the medical aspects and the likelihood of success.

In recent years there has been little attention given to evaluating the cost-effectiveness of tubal surgery and IVF. One reason may be the difficulty in performing randomized trials comparing these two treatments because they have been incorporated into clinical practice and there are preferences for one or the other depending on the viewpoint of the clinician. Consequently, equipoise no longer exists making it difficult for a physician to randomly allocate their patients into a treatment arm they believe will not give the patient the best chance to achieve a pregnancy. Difficulties will also be encountered with patients accepting randomization because of their belief that IVF is the solution to their infertility. Consequently it is more realistic to perform a cost analysis with two comparable cohorts while trying to avoid bias from external factors such as physicians' recommendations or patients' ability to pay for the treatment (7).

The objective of this study was to evaluate the cost of tubal factor infertility when treated with

laparoscopic surgery according to our hospital policy and compare it to the cost of IVF treatment.

MATERIAL AND METHODS

Background

At the Reproductive Medicine Center, Sahlgrenska University hospital, both IVF treatment and tubal surgery are performed within the publicly funded system. All patients with diagnosed tubal infertility are assessed and the same group of physicians makes the recommendation for treatment. The treatment policy is that only patients with mild or moderate tubal pathology (8) are considered for surgical treatment, which is performed laparoscopically. The rest of the patients (who comprise a larger group) can be treated with IVF. The majority of patients referred for treatment are from a larger region. In our study, these referred patients were included in the IVF group and represents the entire spectrum of tubal disease involving mild, moderate, and severe grades of tubal damage.

Study Population

From September 1993 to December 1997, all patients with tubal factor infertility commencing treatment at the Reproductive Medicine Center, Sahlgrenska University hospital, were considered for inclusion in this study. Couples with unexplained infertility, male factor infertility, and severe endometriosis and/or ovulation disorders were excluded. This retrospective cohort design was chosen for logistical and patient compliance reasons as previously discussed. The two groups of patients were followed from initiation of treatment until they had completed a full course of treatment or chose to discontinue their treatment as described below. A live birth was recognized as the end point of this study. Additional cycles or live births were not included in the analysis.

In the tubal surgery group, the medical charts of all patients who had undergone laparoscopic salpingostomy, fimbrioplasty, or salpingolysis during the study time period were reviewed. Patients with a history of at least 1 year of infertility and tubal factor as the sole cause for infertility were included in the surgery cohort for further analysis. All patients were classified according to tubal score I–II and/or adhesion score I–III (8), implying a fairly good prognosis. The minimal follow-up time after surgery was 2 years

for all patients. A second-look laparoscopy was recommended when extensive adhesiolysis had been performed and the risk of recurrent adhesions was considered high.

In the IVF treatment group, all patients who were diagnosed with tubal factor as the main cause of infertility during the same time period were considered for inclusion in the study. The majority of patients were referred directly from a larger region, as described previously, and had tubal disease ranging between mild, moderate, and severe categories. However, referred patients were not classified according to tubal and adhesion scores, thus precluding comparison between patients with only mild and moderate damage. If male factor infertility requiring intracytoplasmic sperm injection was present, the couple was excluded from the study. In no case was a patient included in both groups. A maximum of two embryos was routinely transferred. In accordance with local policy at the unit, a completed course of treatment with IVF consisted of a maximum of three stimulated IVF treatment cycles leading to replacement of embryo(s) unless a live birth was achieved after the first or second treatment cycle in which case the treatment was considered complete. If surplus embryos from one cycle were cryopreserved, the cycle with replacement of these frozen-thawed embryos was considered as part of the original stimulated cycle. If a stimulated cycle did not result in embryo replacement, the cycle was not counted as one of the three cycles required for complete treatment, which explains why 36 patients started four or more cycles (see Table I). Patients who chose not to undergo a completed course of treatment had a follow-up period of at least 2 years after the last visit to the clinic. This follow-up period also included patients who chose not to have their cryopreserved embryos transferred. Data for these IVF treatments were obtained directly from the hospital IVF database.

Table I. Distribution of Started Stimulated Cycles Among 464 Patients^a

Rank of cycle	No. of patients	No. of embryo transfers	No. of cancelled cycles
First	464	423	41
Second	285	259	26
Third	153	131	22
Fourth	29	21	8
Fifth	6	5	1
Sixth	1	1	0

^a Eleven patients had no embryo transfer at all, 3 of these patients started 2 cycles each.

Patients in both the tubal surgery and IVF groups had undergone similar diagnostic evaluation prior to treatment, including semen analysis, serum hormonal measurements (progesterone and prolactin) hysterosalpingography, and/or laparoscopy. The costs for these pretreatment procedures were not included in the study. In cases of tubal disease in the tubal surgery group, in which the diagnostic laparoscopy was converted to operative laparoscopy for treatment, the cost of this additional surgical procedure was included in the total operating time.

Cost Analysis

To determine the costs for the treatments and interventions, standardized hospital charges were used. These charges, which are partly set according to diagnosis-related groups, are routinely used for invoicing costs between departments within the hospital and for referred patients. These costs, which were divided into direct medical costs and indirect morbidity costs (9), were calculated and compared with the outcome of the resulting pregnancies. Direct medical costs included costs for the treatment itself while the indirect morbidity costs were the costs that accrued as a result of the treatment such as costs for spontaneous abortion or cost for delivery. Indirect nonmedical costs such as for travel, sick leave during treatment, or other patient expenses were not included, nor were costs of neonatal care.

For patients undergoing tubal surgery, the duration of surgery was calculated from the time from induction of anesthesia until the patient was transferred from the operating theatre to the postoperative care unit. From the individually recorded time for each patient, the cost per minute was calculated using the hospital charge rate from 2001. No disposable instruments were used during surgery. The mean post-operative time for hospitalization in the regular gynecological department was 2 days. Hence, the hospital charge for 2 days was used to calculate the mean cost for each surgery. No postsurgical complications requiring additional interventions or hospitalization were recorded. After each intervention, the patient was scheduled to have one follow-up visit and the costs were calculated accordingly.

The costs of medication given to patients undergoing IVF were calculated using the mean cost of a standardized ovarian stimulation protocol, which included pituitary downregulation with a gonadotrophin releasing hormone-analogue and recombinant follicle stimulating hormone (r-FSH), (the only

Table II. Pregnancy Outcome in Each Group for the Study Period

	IVF (<i>n</i> = 464)	Tubal surgery (<i>n</i> = 61)
Total pregnancies	335	35
Spontaneous abortion	82	8
Ectopic pregnancy	14	10
Live birth	239	17
Singleton	188	17
Twins	51	0

FSH preparation currently available in Sweden). The charge for IVF treatment set by the hospital was for the total treatment, which includes follow-up visits. Owing to incomplete registration of patients treated for complications, such as ovarian hyperstimulation syndrome (OHSS), the costs for this complication could not be determined and were not included. When estimating the cost of twin deliveries, the hospital charge for delivery-with-complication was used.

The effectiveness of the procedures was calculated as the number of deliveries per treatment and per patient. The cost-effectiveness of the two procedures was calculated as the total cost associated with the procedures divided by the number of deliveries. A twin live birth was considered as only one delivery.

The outcome of the cost analysis is presented as the average cost per patient and the average cost per delivery for the two groups. All costs were estimated according to charge-out rates for 2001 and converted from Swedish krona into U.S. dollars (U.S.\$), with the conversion rate of U.S.\$1 = 9.0 Swedish krona.

RESULTS

Tubal Surgery Group

During the study period, 61 patients who underwent laparoscopic tubal surgery were eligible for

inclusion in the study group. Salpingostomy was performed in 32 and fimbrioplasty in 5 cases, while salpingolysis was the sole procedure in 24 cases. A total of 29 patients underwent a second-look laparoscopy. No cointervention, such as ovarian cystectomy or myomectomy, was performed. The mean duration of surgery was 116 min for the first procedure and 64 min for the second-look laparoscopy. No complications were recorded. During the follow-up period of at least 2 years, pregnancy was confirmed in 35 patients leading to 17 singleton deliveries. Eight patients had spontaneous abortion and 10 patients had ectopic pregnancy. The age of each patient was identified at the date of the first surgical treatment and the mean age in the group was 33 years (range = 23–43 years). The pregnancy outcome of the surgical treatments can be found in Table II. Data for calculation of costs can be found in Table III. The numbers indicated in the table are the numbers of interventions performed and the concomitant costs.

IVF Group

In the cohort of patients treated with IVF during the same period, 464 women started 938 stimulated cycles leading to 840 cycles of transfer with fresh embryos and subsequently, 221 cycles of transfer with frozen-thawed embryos. Eleven patients had no stimulated cycle that resulted in an embryo transfer. All patients who underwent IVF treatment contacted the clinic to report the results of their cycles. The treatments resulted in 335 pregnancies and 239 deliveries among which were 51 sets of twins. There were no triplet deliveries. There were 82 spontaneous abortions and 14 ectopic pregnancies in the group. The age of each patient was identified at the starting date of the first IVF treatment and the mean age in the group was 33 years (range = 22–40 years). The pregnancy outcome of the IVF treatments can be found in Table II.

Table III. Calculation of Costs of Tubal Surgery and Subsequent Interventions

	Unit cost (U.S.\$)	<i>n</i>	Total cost (U.S.\$)
Direct medical costs			
Hospitalisation in gynaecological ward	600	90	54000
Total duration of primary surgery (minutes)	18	7080	127440
Total duration of second-look laparoscopi (minutes)	18	1850	33300
Follow-up visits	181	90	16290
Indirect morbidity costs			
Care in connection with spontaneous abortion	907	8	7256
Care in connection with ectopic pregnancy	2577	10	25770
Maternity care	611	17	10387
Singleton deliveries	2020	17	34340
<i>Total direct and indirect costs</i>			308783

Table IV. Calculation of Costs of IVF Cycles and Subsequent Interventions

	Unit cost (U.S.\$)	<i>n</i>	Total cost (U.S.\$)
Direct medical costs			
Completed IVF cycles with transfer of fresh embryos	2632	840	2210880
Cycles interrupted during stimulation	837	38	31806
Cycles interrupted after egg pickup	1782	60	106920
Cycles with transfer of frozen-thawed embryos	1190	221	262990
Medication for ovarian stimulation	1167	938	1094646
Indirect morbidity costs			
Care in connection with spontaneous abortion	907	82	74374
Care in connection with ectopic pregnancy	2577	14	36078
Maternity care	611	239	146029
Singleton deliveries	2020	188	379760
Twin deliveries	3230	51	164730
<i>Total direct and indirect costs</i>			<i>4508213</i>

Data on the distribution of started cycles are provided in Table I. Data for calculation of costs can be found in Table IV. The numbers indicated in the table are the number of interventions performed and the concomitant costs.

Cost Analysis

The difference in average cost between the two treatments was larger for cost per patient than for cost per delivery, as seen from Table V. The total cost per patient was U.S.\$5,062 after tubal surgery and U.S.\$9,716 after IVF treatment. The total cost per delivery (i.e., per delivery, not per child) was U.S.\$18,164 for tubal surgery compared to U.S.\$18,863 after IVF treatment.

DISCUSSION

In many countries, the treatment of infertility is given relatively low priority, particularly in those with publicly funded health care. Almost 50% of costs for IVF treatments in the Nordic countries are privately financed by patients (10) despite the fact that health

care is financed by national health services in these countries. Also, in the U.S.A. where a large private sector exists, it is rare for infertility treatment and IVF in particular, to be included in private health plans. As a result, infertility treatments have to compete with health services having higher priority for the necessary resources. Although mean cost-effectiveness ratios alone are not recommended to be used to set priorities among different sectors of health care, they may well be used to guide the best use of financed resources (11,12).

The primary difficulty when undertaking an economic analysis is to identify and define the costs that should be included in the study. In the literature, *direct costs* are defined as transactions and expenditures for medical or nonmedical products and services. *Indirect costs* are those that may occur because of morbidity. In our study we have chosen to define *direct medical costs* as medical costs ensuing from the treatment procedure itself, and *indirect morbidity costs* as the costs that originate from the outcome of the treatment. This calculation of costs requires identification of which costs that are less likely to change once a treatment has begun and those that are more dependent on the outcome and success of the treatment. The cost per patient may be a useful figure for comparing how many patients that can be treated under a given budget. For our study we chose to calculate the cost per delivery and not cost per born child to avoid over-interpretation of IVF treatment results which may be favored because of the higher incidence of twin births. Indeed, twin births may be regarded by some as an unfavorable outcome, considering the increased morbidity and mortality and the associated costs.

Like many authors of studies of economic analysis, we too experienced considerable difficulty in

Table V. Cost Analysis for Tubal Surgery Versus IVF

	IVF	Tubal surgery
Total patients	464	61
Total deliveries	239	17
Delivery per patient (%)	51.5	27.9
Costs (U.S.\$)		
Total	4508213	308782
Per patient	9716	5062
Per delivery	18863	18164

identifying the true costs and, therefore, were forced to use hospital charges. Charges are, by definition, the result of costs as they are measured by the market and reflect costs only for those who pay for them (9). In our clinical setting, the charges have been set by the hospital authorities and are used to submit invoices for treatment within the institution and between departments. Therefore we can only presume that these charges are fairly accurate in describing the true costs for the different interventions.

Several studies have reported conflicting results in the cost-effectiveness of tubal surgery versus IVF (5,13–15) but all agree that IVF is at least as cost-effective as tubal surgery (16). A study from the U.S.A. in 1996 (17) concluded that IVF was both slightly more effective and more cost-effective than tubal laparoscopic surgery. In this study women treated with tubal surgery were of lower socioeconomic status than those treated with IVF so that the results in that study were influenced by economic considerations since only tubal surgery was covered by insurance plans. This was not the case in our study because both groups of patients were treated under the same publicly funded system. In Sweden, as in many other countries, tubal surgery used to be performed in many more institutions within a region than IVF. Gynecologists in these institutions may have chosen surgical treatment for their patients simply because of easier availability. However, during the last decade, there has been a shift from surgery to IVF, implying that tubal surgery even in cases of mild damage is more or less abandoned in non-university-based institutions. It has also been shown (18) that a high grade of tubal damage is also associated with a lower pregnancy rate after IVF. The failure to conceive after surgical reconstruction very often results in a referral to IVF treatment. Patients with a poor prognosis after surgery are at increased risk for ectopic pregnancy; they lose valuable time and might have a reduced chance of achieving a term pregnancy if IVF treatment is delayed by an inappropriate surgical tubal repair. In contrast, in our study the patients found eligible for tubal surgery were diagnosed and selected within a single institution where both surgical treatment and IVF are performed. The clinic has long-standing experience not only in IVF but also in tubal surgery, and the criteria described by Mage *et al.* (8) were followed strictly to select patients for tubal surgery. We believe that this is a very important factor when considering the results of our study. Patients treated with tubal surgery in the first instance because of treatment availability and not on the basis of strict

medical indications will, if the treatment fails, incur a proportionately higher cost for their infertility treatment. This approach is of no benefit to either society or the patient. But it should not be overlooked that a successful tubal reconstruction procedure has advantages over treatment with IVF in that the woman has a chance to conceive in each cycle without requiring further treatment. Therefore the aim of the patient selection process for tubal surgery must be to identify those in whom this treatment can provide realistic benefit. The reverse pattern, patients asking for tubal surgery after failed IVF, is becoming increasingly more common and demonstrates the importance of a proper infertility workup to select patients eligible for surgery.

In the group treated with IVF, patients with severe tubal pathology were included and among these patients it is most likely that cases with hydrosalpinx were present. It has been shown (19) that in patients with bilateral hydrosalpinges that are large enough to be visible on ultrasound, salpingectomy prior to IVF increases the pregnancy rate. It may therefore be suggested that if patients in the IVF group had been screened for hydrosalpinx and pretreated with salpingectomy the outcome would have been different. Naturally, if this intervention had increased the number of deliveries in the IVF group, it would also have increased the costs because of the additional salpingectomy. Consequently, the detection of the overall effect on the cost analysis is difficult to predict.

In the IVF group, 11 patients had no embryo transfer and hence no chance of a pregnancy or delivery. The policy of the clinic is to offer three publicly funded stimulated cycles to patients entering the IVF program unless a live birth is achieved after the first or second cycle, including cycles with transfer of frozen-thawed embryos. We found that only 71% (330/464) of the patients commencing IVF treatment actually went through the complete treatment program. Similar figures on how patients utilize the offered programs have been published in other centers (20). The reason for patients not completing the program at our center has been shown to be mainly emotional; patients find the treatment too tiresome (21).

We would like to point to the fact that the cost of IVF in our study may be underestimated because we have not included the costs of OHSS or neonatal care. The incidence of moderate to severe OHSS requiring hospitalization in this group of patients could be estimated at 1–2% of stimulated cycles (22). Applying these figures to our setting would suggest that for the 840 embryo transfers there would be 13 cycles (i.e.,

840 $\times$ 1.5%) requiring treatment for 2–3 days in a gynecological ward because of OHSS. This complication would add U.S.\$82 (13 cycles $\times$ 2.5 days $\times$ U.S.\$600/239 deliveries) to the cost of a live birth. Since we have no data to support these assumptions, we have chosen not to include them in the results. The lack of data on costs for neonatal care is the main reason for not including these costs. Although IVF treatment in our study did not result in multiple births of higher order than twins, the patients treated with tubal surgery had no twin births at all suggesting that our cost analysis may be biased towards IVF. Single embryo transfers would certainly decrease the risk of twin pregnancies (23) and by identifying patients at high risk of multiple birth and applying single embryo transfer to these patients the rate of multiple birth may be reduced by up to 50% (24). The overall effect on pregnancy and twin rates from replacing a single blastocyst as compared with a single cleavage stage embryo still needs further evaluation particularly in how these new treatment regimes will influence the cost analysis.

Because of the retrospective design of the study, individual time periods for sick leave were not possible to determine and therefore were not included in the analysis. Since all surgery was performed laparoscopically, with a recommended recovery time of 1 week and patients after IVF in our setting usually stay off work for 4–7 days after egg pickup we assume that these costs were similar for the two groups. However, since the patients in the IVF group underwent in mean two treatment cycles, this assumption may also show to be an underestimation of the costs connected with IVF treatment.

We have shown that the cost per delivery of tubal surgery in appropriately selected cases is comparable to IVF for patients with tubal disease when treated by the same group of fertility specialists under the same publicly funded health care system, in which only medical considerations have dictated the choice of treatment. If selection in this manner had not been undertaken and patients with severe tubal disease had been treated with tubal surgery instead of IVF the differences in cost would likely have been greater. In contrast, if all patients including severe, moderate, and mild tubal disease, instead, had been treated with IVF, we do not believe that the cost per live birth would have been significantly different from the results in this study. The patients in our study were treated under the same publicly funded health care system, which means that they do not pay for either treatment or medication. We are well aware

that conception rate and time to conception are very important factors to be considered when it comes to counseling in the individual case but the result in this study should be of great interest also to health providers. The cost per patient is almost doubled for IVF treatment, but since the success rate is higher, the cost per delivery evens up in the two groups. However, if we overlook the cost per delivery and only consider the effectiveness of treatment, IVF is more effective. If patients were free to choose treatment only with regard to the chance of having a baby, most patients would choose IVF treatment before tubal surgery. Nevertheless, tubal surgery has indisputable benefits for the patient if the infertility is “cured” by the intervention. A successful tubal repair gives the patient the possibility of conceiving more than once without further treatment. It also gives the couple the psychological advantage of being able to conceive spontaneously. The very low risk of multiple pregnancies is also a factor in favor of tubal surgery. To optimize the use of resources, it is of utmost importance to ensure that patients who will benefit from tubal surgery are appropriately selected. If this objective is achieved, tubal surgery will continue to have a role in the treatment of infertility from tubal disease.

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