

Cost-effective infertility care

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Cost-effective healthcare has become a principal paradigm in all areas of medicine. In order to establish cost-effective care, clinical outcomes under various cost conditions have to be examined. Such a process cannot be static since it has to consider ever evolving treatments and outcome results. In infertility, the evaluation of cost-effective care should be simpler than in most other areas of medicine since treatment end-points are easily defined. Nevertheless, the field is lagging in the establishment of cost-effective treatment algorithms. In this review, an effort is made to define the current state of the art of cost effective infertility care, to suggest steps that can be taken to drive the process forward and to encourage the introduction of even limited processes to further the concept of outcome-dependent cost assessment within a practice setting. The limited availability of resources mandates their judicious use throughout medicine. In a field like infertility, by many (rightly or wrongly) perceived as ‘elective’, the judicious use of resources seems even more necessary since it would permit the treatment of larger patient populations than have currently access to care without further expense to third-party payments.

Key words: cost assessment/infertility care

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Introduction

In a ground-breaking decision, the US Supreme Court recently defined the ability to reproduce as a basic life activity. This case reaffirmed earlier lower court decisions which had come to define infertility as a disability under the Americans with Disability Act (ADA) (Gleicher, 1998a).

Based on an earlier lower court’s decision, the City of Chicago had chosen in 1997 to settle a class action suit brought against the city by a policewoman who had claimed discrimination under ADA because the city had not offered her medical insurance for infertility services. This settlement retroactively and prospectively established such insurance coverage for the plaintiff, the class and all city employees (Gleicher, 1998a).

The more recent Supreme Court decision makes it quite likely that the fear of similar lawsuits will very rapidly expand insurance coverage for fertility services, which currently are only rarely offered. As the few states with legislatively mandated insurance coverage have demonstrated, when the insurance industry is forced to cover infertility services, a search for cost-effective services ensues (Gleicher, 1998b). The following is a conceptual discussion of cost-effective infertility care.

Some principles of infertility care

The treatment of infertility has made substantial progress over the last two decades. The more rapid the medical progress in a particular speciality, the less likely has the parallel process of maintaining cost-effective care kept pace. The excitement of medical progress only too easily overcomes cost concerns. Infertility care is a classical case in point.

A number of important discoveries have revolutionized the treatment of infertility. Intrauterine insemination (IUI) (Lalich *et al.*, 1986), in-vitro fertilization (IVF) and other assisted reproductive technologies (ART) (Stephoe and Edwards, 1978) or intracytoplasmic sperm injection (ICSI) (Palermo *et al.*, 1992) all revolutionized healthcare for selected patient populations who, prior to their clinical application, either had no or only very little chance of conception. Sadly, however, even today, many years after the wide introduction of all of these treatment options into routine fertility care, there is still no definition of their respective positions within a cost-effective treatment algorithm. The same can be said for tubal surgery

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Table I. Selective contradictory practice patterns in infertility

Laparoscopy as routine diagnostic test	yes/no
Hysteroscopy as routine diagnostic test	yes/no
Hysterosalpingogram/gynaecoradiological procedure as routine diagnostic test in place of laparoscopy/hysteroscopy	yes/no
Post-coital test as routine diagnostic test	yes/no
Endometrial biopsy as routine diagnostic test	yes/no
Sperm antibodies as routine diagnostic test	yes/no
Immunological testing for implantation failure	yes/no
Immunological treatments for implantation failure and recurrent pregnancy loss	yes/no, or with what treatment choice(s)
Clomiphene citrate: monitored versus unmonitored (ovulation prediction kit)	
Number of clomiphene citrate cycles before switch to gonadotrophins	3–4 or 4–6
Clomiphene citrate for females aged >38 years	yes/no
Progesterone substitution in luteal phase	yes/no
Fulguration by laparoscopy for mild endometriosis	yes/no
Tubal surgery for moderate/severe tubal disease versus IVF	
Intrauterine insemination(s) with ovulation induction cycles	yes/no
One versus two intrauterine inseminations per ovulation induction cycle	
Number of gonadotrophin cycles before advance to IVF	3–4 or 4–6
Number of IVF cycles	up to 4, or more
IVF versus GIFT, ZIFT or other ART procedures	

IVF = in-vitro fertilization; GIFT = gamete intra-Fallopian transfer; ZIFT = zygote intra-Fallopian transfer; ART = assisted reproductive technologies.

(Benavida *et al.*, 1995), the value of surgery in cases of endometriosis (Shushan *et al.*, 1995; Marcoux *et al.*, 1997) and, probably, a large majority of treatment modalities currently widely offered to female and male patients with infertility.

The assessment of cost-effective care is impossible without the prior evaluation of *effective* care. Outcome assessment of specific treatment options is, therefore, a precondition to any evaluation of *cost-and-effective* care. The multifaceted nature of most medical conditions greatly complicates medical outcome reporting. Infertility, however, offers rather simple end-points for outcome reporting: couples either conceive and have a child or they do not. Consequently, even if the couple's aetiological circumstances are multifaceted in nature, outcome assessment in infertility care is potentially simpler than in most other medical conditions. The evaluation of cost-effective infertility care should therefore be simpler than the establishment of cost-conscious care in most other areas of medicine.

Why is infertility care so inhomogeneous?

Table I is an attempt to present an (incomplete) list of clinical practice patterns which are, by many, considered to be contradictory in nature and, yet, each finds wide support amongst competent practitioners. They basically encompass the entire field

of infertility care and are rather unprecedented in their divergence for any practice area of medicine.

The answer probably lies in the fact that most infertility treatments have entered the clinical mainstream without prior outcome assessment. IVF (Steptoe and Edwards, 1978), IUI (Lalich *et al.*, 1986) and ICSI (Palermo *et al.*, 1992), all represented breakthrough technologies which, with great likelihood, were effective in achieving pregnancy in couples who previously had failed available treatment modalities. However, these techniques (and many others) then became the victims of their own success: once found to be effective in some, their application became indiscriminate (Grimes, 1993). Their evaluation as clinically effective and cost-effective treatment modalities became therefore almost impossible.

In contrast to these experiences in infertility care, most other medical progress is incremental and not revolutionary in nature. Incremental progress is usually more controlled, will lead to a more selective application of new technology and, therefore, to a better opportunity of proper prior outcome assessment.

Infertility care as a whole has become the victim of its own very rapid success. It now seems time to take a breath and make up for missed past opportunities by carefully evaluating the true outcome statistics for various infertility treatments. Without such a process, cost-effective infertility care will remain a distant goal.

Cost-effective infertility care: what does it mean?

The definitions of cost-effective healthcare is the achievement of an attainable treatment goal at the lowest possible expenditure of resources and, therefore, lowest possible cost. Van Voorhis *et al.* (1997) recently well described the various forms of economic analyses that can be applied within the healthcare field. In limited attempts to define cost-effective care within the infertility arena, this more often than not has only meant the calculation of total presumed cost per pregnancy established, following a specific infertility treatment (Wolner-Hansen and Rydhstroem, 1998). We, like others, have been guilty in assuming that conception does, in fact, represent an appropriate end-point for infertility care (VanderLaan *et al.*, 1998). Such an assumption is, however, nonsensical because it encourages medically and economically unsound practice patterns.

Every practitioner is motivated to maximize outcome. If conception is the principal outcome parameter, practitioners will be encouraged to maximize conception rates which indiscriminately will also result in higher multiple conception rates. Multiple conceptions, in turn, carry higher clinical risks than singleton conceptions and, therefore, with it, also higher obstetric and neonatal costs (Callahan *et al.*, 1994; Collins *et al.*, 1994; Neuman *et al.*, 1994).

The appropriate outcome end-point for infertility treatment is, therefore, birth and/or discharge of mother and neonate after birth rather than conception. Anything else is self-defeating in its incentives and deceptive in its accuracy of cost assessment.

Providers of fertility services usually discharge their pregnant patients early in pregnancy into the hands of obstetricians. They therefore argue that they cannot be held responsible for pregnancy outcomes. The literature confirms that the outcome of multiple gestations can vary based on the quality of obstetric care (Luke, 1994). The literature, however, is also rather unanimous in describing the increase in prematurity and severe prematurity as a consequence of multiple implantations and independent of quality of obstetric care (Jewell and Yip, 1995). In fact, the literature is now also unanimous in making the point that even a selective embryo reduction procedure does not fully reduce the prematurity risk (Alexander *et al.*, 1995; Cusick and Gleicher, 1995; Silver *et al.*, 1997), thus confirming the importance of minimizing multiple implantations. The fertility specialist therefore carries a principle responsibility for obstetric outcome.

This means that the final cost of infertility treatment cannot be assessed until maternal and neonatal outcome are assessed. However, it also means that current payment incentives for infertility services are illogical and reward infertility specialists for the wrong treatment outcomes.

Aligning incentives: the new provider organization

The Japanese taught the world that absolute quality control at every step of assembly was the only way to produce high-quality, low-cost products. Until this was recognized, manufacturers traditionally reserved the quality control process for the time when a product came off the assembly line. Such post-factum attempts at quality control are less effective and more costly than prevention of defects in the first place. Consequently, absolute

quality control at each step has become the dogma in the production of high quality products at lowest possible cost.

With a hopefully healthy mother and child as the end-product of infertility care, there is an analogy to manufacturing in this 'production process'. Since three different medical specialties contribute to the end-product, the medical care expensed by each of these specialists can be seen as individual stations of a product assembly line. Only if each 'production step' is meticulously performed will the end-product be flawless. Moreover, only if no 'post-production repairs' (e.g. the use of a neonatal intensive care unit) is required, will 'the product' be produced in a cost-effective fashion.

The infertility specialist initiates the process and affects the timing, as well as the occurrence, of pregnancy. This specialist's responsibility in regards to timing of conception is, in fact, considerable and often overlooked. For example, women with diabetes mellitus affect the magnitude of their risk to have offspring with congenital anomalies by controlling blood sugar levels in early pregnancy (Buttino and Gleicher, 1998). Absolute quality control of infertility care therefore mandates that the fertility specialist initiates pregnancy in diabetic women only once adequate blood glucose control has been established. This is just one amongst many examples describing the fertility specialist's responsibility for preconception counselling, whether in regards to maternal medical or the family's genetic history.

The fertility specialist obviously also affects the occurrence of pregnancy. Better care will usually achieve pregnancy quicker, though this paradigm should be considered as somewhat more complex than that. The definition of 'better' care should not necessarily be equated with more 'aggressive' care. More aggressive care may result in quicker establishment of pregnancy and higher pregnancy rates per treatment attempt; however, more aggressive care can also lead to a higher incidence of multiple implantations. Better care should, therefore, be defined as the proper balance between attempts to achieve pregnancy quickly and efficiently; however, with as low a multiple implantation rate as is possible (Collins, 1994).

To return to the manufacturing analogy, multiple implantations represent a flaw at the first step of the assembly line which will require the expenditure of considerable effort and cost to be 'repaired' during later steps, if such repair is at all possible. Since we know that multiple gestation carries risks that may not be preventable even with the best obstetric and neonatal care, the infertility specialist may have damaged the end-product beyond the possibility of repair and also created significant additional cost (Goldfarb *et al.*, 1996). This has been well recognized in Europe, though not to the same degree in the USA. Especially in the Scandinavian countries clear efforts towards 'less aggressive' care are underway in attempts to limit the number of multiple births.

Obstetricians and/or high-risk obstetricians (perinatologists) as well as neonatologists often also significantly contribute to the final outcome. Thus, they are an integral part of the 'assembly line' that leads to the final end-product, a hopefully healthy mother and offspring. Since three different specialties are involved in achieving this outcome, it would seem important to encourage all three specialties to co-operate closely. Paradoxically, this does not happen in today's healthcare system.

In fact, current reimbursement structures reward all the wrong incentives.

The fertility specialist is rewarded for quick establishment of pregnancy and high pregnancy rates but is not economically punished for multiple pregnancy rates. The fertility specialist is given neither the incentive to provide proper preconception counselling nor to transfer often high-risk pregnant infertility patients into the care of high-risk obstetricians (perinatologists). Insurance coverage and/or traditional physician referral patterns often irrationally mandate the return of pregnant patients to their primary care obstetrician/gynaecologist even if they are judged to represent high-risk pregnancies. The healthcare system has yet to understand that infertility patients overall represent a high-risk patient population, whether they carry singleton pregnancies, low order multiples or have undergone selective reduction to a singleton or low order multiple gestation (Schenker and Ezra, 1994; Evans *et al.*, 1995).

Obstetricians and neonatologists, in turn, often fail to understand the circumstances that lead to pregnancy of previously infertile couples. For them these pregnancies are just other conceptions, often failing to recognize the high-risk status of a seemingly uncomplicated pregnancy. Or they perceive themselves on the receiving end of a reckless decision-making process between fertility expert and patient, which has led to a high-risk pregnancy situation that could have been avoided in the first place.

In doing so, they overlook that fertility experts, like other physicians, practice under full informed consent rules and are therefore obligated to consider patient wishes. For example, older patients are especially desirous of (low order) multiple births, seeing this as an opportunity to catch up on completing a family. This desire for multiple gestations is correlated with female patient age and length of infertility and is based on full awareness of outcome risks (Gleicher *et al.*, 1995). A couple's readiness to assume more risk with regard to a multiple gestation may, therefore, be much more than just a seemingly reckless act. It may, in fact, be a conscious choice by a well-educated couple, which an infertility provider has no right to resist as long as the requested practice patterns are within generally accepted standards of care.

These complexities of infertility care call for a fully integrated provider process that starts with preconception counselling and ends with discharge of mother and child after hopefully normal birth. Cost-effective infertility care will not be achieved until a new format of provider organization has been created which sees infertility care as such a continuum. Third-party payors would be well-advised to support the development of such longitudinally integrated provider organizations by aligning payment incentives accordingly. Ideally, providers should not be paid for individual components of the production process but only for the end-product. Such a payment system would align incentives between the three medical provider groups because they all would benefit from the discharge of a healthy mother and child with the least amount of required care and would suffer financially from adverse outcomes and complications at any treatment stage.

Patient satisfaction is crucial

Cost-effective care has to satisfy patient demands. Without high levels of patient satisfaction, cost-effective care is neither an

acceptable goal nor does it satisfy the minimal demand for quality of care. Quality of care always contains, as an important component, a high degree of patient satisfaction (Cleary and Edgman-Levitan, 1997).

Like most medical care, infertility care is information-driven. Unlike with much other medical care the infertility patient is, however, often well educated about the process of care and enters treatment, therefore, with specific expectations. Since the treatment of infertility does not represent an emergency situation, the patient has ample time to self-educate. Moreover, since the definition of infertility as an attempt to conceive for >1 year (Jake and Jewelewicz, 1991), requires full awareness of the process, infertile couples reach treatment after a conscious period of attempts at self-treatment. All of this creates a very knowledgeable consumer who not only expects treatment results quickly but often has preconceived notions of how those results should be obtained. It is obvious that patients in medical emergencies face care providers quite differently since they do not have such an opportunity to prepare.

Patient satisfaction therefore not only depends on how well infertility treatment is provided but what the expectations of the patients have been in the first place. Even a very high quality level of patient care will therefore not lead to patient satisfaction if patient expectations are not met. The definition of patient expectations should therefore be an integral part of a couple's entry into the fertility treatment process. Once expectations are defined, those expectations can either be met by the provider or, if this cannot be done, this needs to be addressed with the couple in the hope that their expectations can be redirected. Failure to do so will result in exceedingly high drop-out rates from treatment (Gleicher *et al.*, 1996a)—a very wasteful use of resources.

If patients expect direct physician involvement at every step of the treatment process and the programme traditionally delegates many functions to clinical staff (ultrasound technicians, nurses, etc.), then even the best level of care by physician extenders will not achieve patient satisfaction unless patients can be re-educated. However, cost-effective infertility care will be difficult to achieve if physicians are required to provide all services.

Programme location

Modern infertility care only rarely requires a hospital facility. In fact, with the exception of major surgery, all other clinical activities can safely be conducted outside of a hospital setting. Programme locations are, therefore, important considerations in developing cost-effective infertility care. For example, in the USA, a hospital-based IVF facility will only rarely be able to compete economically with a community-based centre because of significantly greater overhead expenses in the former set-up. Similarly, outpatient or office-based surgery will almost always be more cost-effective than hospital-based operations.

Infertility providers in the USA have, therefore, increasingly abandoned hospital-based locations in favour of community-based set-ups. This trend can be expected to continue as fee structures become increasingly competitive and package pricing for infertility services, which has to include facility charges, represents an increasingly prominent contracting format.

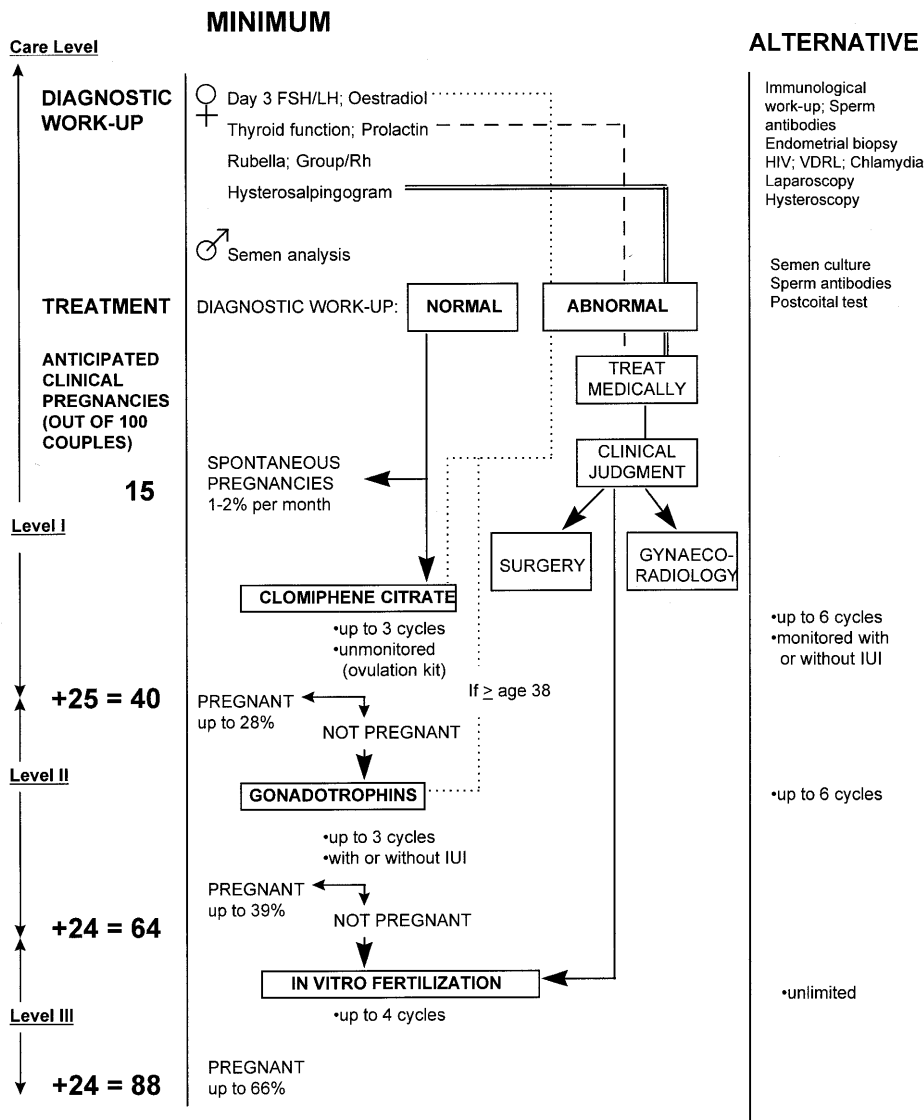


Figure 1. Treatment algorithms for infertility and expected pregnancy rates (cumulative).

Treatment algorithms

It is widely assumed that treatment algorithms drive the cost-effectiveness of infertility care. To a large degree this is correct. It would, however, be a mistake to assume that cost-effective infertility care is exclusively driven by such treatment algorithms. The neonatal intensive care costs of a single very premature infant can exceed the total infertility treatment costs of hundreds of couples. This example alone should explain why treatment algorithms are only addressed after other issues that affect cost-effective infertility care have been discussed.

Treatment algorithms not only define cost but also quality of care. Table I outlines many of the differences that currently still characterize diagnostic and therapeutic steps in infertility care. Figure 1 summarizes a treatment algorithm which, while certainly not universally accepted, has proven acceptable to many providers in the USA and has been accepted by the insurance industry in states with

mandated insurance coverage as the basis for contractual agreements (VanderLaan *et al.*, 1998).

Based on this treatment algorithm, ~80% of couples who proceed through all treatment steps can expect to conceive. Figure 1 summarizes conception data which are compatible with published data for individual treatment modalities though, to the best of our knowledge, no longitudinal life-table analysis of this (or any other) treatment algorithm has ever been performed. We are currently in the process of prospectively analysing a patient cohort going through exactly the algorithm outlined in Figure 1. Preliminary results from this study are, in fact, supportive of the outcome data described in the figure, though with the caveat that patients who go through infertility treatment unfortunately experience considerable drop-out rates at each treatment step (Gleicher *et al.*, 1996a). A correct informed consent, therefore, should include the explanation that an 80% chance of conception applies only to couples who stay in the course of treatment.

Treatment-independent fertility rates

To assess efficacy of treatment, the therapy’s outcome effectiveness has to be calculated by subtracting a patient’s treatment-independent pregnancy rate from the treatment’s overall pregnancy rate. A number of studies have demonstrated that in an average infertile population, treatment-independent pregnancy rates are in the vicinity of 1–2% per month (Collins *et al.*, 1995; Gleicher *et al.*, 1996b). Some data suggest that they can climb even higher if patients are given rest cycles between ovarian stimulation cycles rather than follow the traditional treatment protocol of stimulating patients in consecutive months. In fact, these data suggest a close correlation between a number of ovarian stimulation cycles (and, therefore, rest cycles) and so-called spontaneous pregnancy rates (Karande *et al.*, 1999).

This raises the question whether these cycles should, in fact, be seen as ‘treatment-independent.’ A significant incidence of spontaneous pregnancy rates has also been reported in women on luteal phase gonadotrophin-releasing hormone (GnRH) agonists in preparation for ovarian stimulation with gonadotrophins. Spontaneous pregnancies have also been reported following gynaecoradiological procedures, even following routine hysterosalpingography. All of these observations suggest first that all so-called treatment-independent pregnancies are not necessarily spontaneous in nature and, second, that the effectiveness of every treatment algorithm can only be assessed if pregnancies in non-treatment cycles, whether spontaneous in occurrence or not, are considered.

This was effectively demonstrated in a prospectively randomized study which compared the traditional infertility algorithm show in Figure 1 to the use of IVF as an initial infertility treatment. While the traditional infertility algorithm was found to be significantly more cost-effective (and efficient), this was to a large degree the consequence of many so-called treatment-independent pregnancies that occurred much more frequently under standard algorithm conditions than in-between IVF cycles (Karande *et al.*, 1999).

Cost of infertility care

The cost to provide comprehensive infertility services will vary based on market conditions and local practice patterns. For example, medical costs are in general lower in most European countries than in the USA. Consequently, it should not surprise that the per case cost of infertility services in the USA exceeds those in most other developed nations, though use of services overall lags.

As Table II summarizes, there are a number of reasons for these differences. The US market is still a largely ‘private’ healthcare market. As managed care assumes a bigger and bigger role, it is likely that many of the characteristics of the US market will come to equate those of the healthcare markets of other developed nations. Moreover, infertility services in the USA are still largely uninsured. Only 13 states mandate often very limited insurance coverage, while in the rest of the USA a large majority of patients go without insurance or with only very limited coverage for infertility services.

Table II. Causes for higher treatment costs in the US

US	Other developed countries
Mostly private; market-driven	Mostly national insurance
Mostly uninsured services	Mostly insured services
High medication costs	Low medication costs
High provider costs	Low provider costs

A recent decision by the US Supreme Court, which defined infertility as a disability under the Americans with Disabilities Act, may change the insurance situation in the USA very quickly (Gleicher, 1998a). Such a change can be expected to lead to a lower fee structure for infertility services as patient volumes increase. This has been well documented in states like Illinois and Massachusetts where relatively comprehensive insurance mandates have existed for years. However, even under such conditions infertility service costs remain high in comparison with other countries, not the least because of dramatically higher pharmaceutical costs for the US consumer in comparison to consumers elsewhere.

Accepting this as a given, the cost of infertility services still vary in the USA within a range of >200% (N.Gleicher, unpublished data). This extraordinarily wide range in cost cannot be explained based on differences in quality of care alone. It has to be based on the previously mentioned discrepancies in practice patterns which often add highly inefficient levels of care. We have identified four areas that lend themselves to considerable potential cost savings without affecting quality of care negatively. They also represent the principal contributing factors for cost differences observed in the US marketplace. We will define those within the three traditional levels of infertility care (Figure 1).

Level I care

This level of care involves diagnostic work-up and initial (mild) ovarian stimulation with clomiphene citrate. Level I care is traditionally administered by the generalist rather than the fertility specialist, though data strongly suggest that the most cost-effective provider system is a unified system that guarantees smooth transition from Level I through Level III care to all patients (VanderLaan *et al.*, 1998). Such a system is characterized by the specialist providing all care, though a competitive system involving generalists in Level I care could be devised if repetition of diagnostic tests can be avoided and initial clomiphene citrate therapy is provided adequately and only for a limited number of cycles (see Figure 1). Poor ovarian stimulation and/or an inefficiently high number of clomiphene citrate cycles obviously unnecessarily raise costs.

The potentially largest cost savings in Level I care come, however, from proper utilization (or better non-utilization) of surgical procedures. Proper utilization of surgical procedures, usually endoscopic procedures, represents the single most significant factor in providing cost-effective infertility care (Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine, 1998).

Routine laparoscopy and/or hysteroscopy is still widely considered an appropriate diagnostic step for every infertility

patient. Relevant diagnostic information can be obtained more cheaply (and probably clinically in a more relevant way) by performing a gynaecoradiological procedure (GRP) instead. In the case of a normal GRP, the probability of clinically relevant tubal disease and/or endometriosis is so low that laparoscopy does not seem further warranted (Gleicher and Karande, 1996; Karande *et al.*, 1996). One has also to wonder about routine performance of diagnostic hysteroscopies under general anaesthesia in an operating room setting, when in-office hysteroscopy, sonohysterosalpingography or a GRP represent so much more cost-effective diagnostic alternatives.

Other laparoscopic and/or hysteroscopic surgeries that seem outdated by contemporary practice alternatives are end-to-end tubal anastomoses for proximal tubal occlusion, which in >90% of cases can be successfully replaced with transvaginal tubal catheterization procedures under radiological control (Gleicher *et al.*, 1993), and distal tubal surgery for moderate and severe hydrosalpinges, which should be replaced by IVF (Benavida *et al.*, 1995; Van Voorhuis *et al.*, 1997). Repeat tubal surgeries represent an ineffective treatment choice because of low pregnancy rates following such surgery. Van Voorhis *et al.* (1998) reviewed the cost of IVF versus tubal surgery in great detail. Their conclusion can be summarized as stating that only totally uneconomic considerations in regards to insurance coverage (surgery being covered and IVF not) may warrant the continuous use of surgery.

Assuming a surgical utilization pattern in accordance with above outline principles, we have been able to reduce surgical utilization to 10–15% of what is customary in the community with no adverse effect on outcome (VanderLaan *et al.*, 1998; N.Gleicher, unpublished information).

Lesser, though still significant, savings in Level I care come from prudent usage of diagnostic tests. For example, the routine use of endometrial biopsies can be challenged. Endometrial biopsies are interpreted with a wide margin of error rendering the test itself questionable. Moreover, since many, if not most, treatment cycles are accompanied by luteal phase support with progesterone, one has to wonder about the clinical usefulness of the test. Yet, many practitioners still use endometrial biopsies as a routine investigative tool on all of their patients.

Limited value has also to be assigned to the so-called post-coital test. At a time when many, if not most, fertility treatment cycles involve intrauterine inseminations and thus bypass the cervix, this test seems redundant.

The utilization of sperm antibody testing has been declining over the last decade. While the evaluation of sperm antibodies was never an exact science, as with post-coital tests, the widening clinical use of intrauterine inseminations seems to have further affected the utilization of this test. It is nevertheless still widely ordered, though it is unclear how a positive test would alter standard infertility treatment.

Cost-effective Level I infertility care should also consider the reduction of many other tests currently widely performed. For example, does a married couple really have to be tested routinely for human immunodeficiency virus (HIV) antibodies, serology, other sexually transmitted diseases and hepatitis if they offer no high-risk history? Or does the severely oligospermic male still need a detailed hormonal analysis, if the only obvious treatment

option is ICSI? And is there still value to expensive hamster egg penetration assays?

In short, enormous cost is currently incurred on unneeded routine testing which neither contributes to the diagnostic accuracy nor improves therapeutic choices. A cost-effective system of infertility care should therefore address unnecessary and costly diagnostic expenses.

Level II care

Patients who have failed Level I care advance into Level II care, which traditionally means the use of exogenous gonadotrophins. Gonadotrophins have two principal indications: they are either used to induce ovulation in females who have failed to ovulate on clomiphene citrate therapy, or they are used empirically on patients who have simply failed to conceive during Level I care, though they may have, in fact, ovulated.

Published data do strongly suggest that such empirical usage of gonadotrophins is effective and results in considerable pregnancy rates (Figure 1). The mechanism(s) of this success is/are unclear. This author has equated the process anecdotally to 'buying more tickets in the lottery,' by inducing the ovulation of more oocytes than in natural or clomiphene citrate induced cycles.

This, however, does not seem to be the only answer. The recent observation that rest cycles in between ovarian stimulation cycles with gonadotrophins results in higher than expected spontaneously occurring pregnancies (Karande *et al.*, 1999) (see above) also point towards a more systemic effect on ovarian function and, possibly, oocyte as well as endometrial quality. It seems telling that the currently, probably most widely applied treatment in fertility care, is basically not understood in its effectiveness.

Our own data suggest that the effectiveness of ovarian stimulation with exogenous gonadotrophins decreases after two to four such cycles (Gleicher *et al.*, 1999). The standard treatment algorithm in Figure 1 therefore depicts only three such cycles. Because of the considerable cost involved in such treatment, ovarian stimulation with gonadotrophins requires careful utilization review. Cost arises from quite a number of possible sources:

Medication costs

After a decades-long monopoly by one manufacturer, two more have now entered the market in the USA. Moreover, different manufacturers offer a variety of gonadotrophin products at rather dramatic price differences. As recently stated by the American Society for Reproductive Medicine (1998), for most indications there appears to be no difference between products. Consequently, it seems appropriate to use the least costly products.

This author recently led the conversion of a very large programme from more costly, primarily follicle stimulating hormone (FSH)-driven products to a cheaper generic human menopausal gonadotrophin (HMG) product (N.Gleicher, unpublished data). A very careful prospective follow-up of women who underwent ovarian stimulation with the HMG product demonstrated no adverse impact whatsoever as a consequence of the switch to the less expensive gonadotrophin. More recently, this author initiated a similar switch to HMG products in our centre's IVF programme. Preliminary 3 month

results demonstrate no adverse outcome in IVF either (N.Gleicher, unpublished data).

Medication dosage

Despite data to the contrary, many practitioners believe that increasing medication dosages will result in better ovarian stimulation. Ovarian overstimulation by gonadotrophins can be life-threatening to the mother and will be especially dangerous if conception occurs during an overstimulated cycle. Overstimulated cycles often result in multiple implantations, further increasing the severity of the maternal overstimulation syndrome. The costs of such overstimulation and of resultant multiples are considerable and often preventable (Gleicher *et al.*, 1999). Even in older women and poor responders, where ovarian overstimulation is of little risk, more medication does not achieve better outcomes. The literature is clear in demonstrating that a dosage of more than six ampoules (450 IU) does not mean more pregnancies. The administration of higher dosages is, therefore, a waste and can be prevented through an appropriate utilization review process. At an average US cost of \$50 per ampoule (75 IU) of exogenous gonadotrophin, the cost savings from a properly devised use review process can be astounding and have been >40% (N.Gleicher, unpublished data).

Treatment length

Like other fertility treatments, exogenous gonadotrophins lose efficiency over time. Data from our own centre suggest that maximal efficiency may be lost as early as after two cycles of gonadotrophin stimulation (Gleicher *et al.*, 1999). These data are supported by other studies (Templeton *et al.*, 1996; Templeton and Morris, 1998) which show a similar decline in treatment efficacy after IVF. Most practitioners, however, still assume similar treatment efficacy up to four or even more cycles. Usage of these medications beyond four cycles would, therefore seem wasteful and can be prevented through a well-designed utilization review process.

Intrauterine insemination

There is evidence that pregnancy rates are higher after ovarian stimulation with exogenous gonadotrophins if such cycles are accompanied by intrauterine inseminations rather than regular intercourse (Chaffkin *et al.*, 1991). Cost-effective care would, therefore, suggest that gonadotrophin cycles be routinely accompanied by inseminations. Van Voorhis *et al.* (1998) recently reviewed in detail the advantage of intrauterine inseminations in conjunction with various ovarian stimulation protocols versus ovarian stimulation with intercourse. The data appear convincing.

Ovarian reserve

Published clinical data on ovarian stimulation with gonadotrophins (fully confirmed by IVF evidence) strongly suggest that pregnancy rates are dismal in the presence of elevated day 3 FSH concentrations in the female (Scott *et al.*, 1989). Considering the extraordinarily high cost of ovarian stimulation cycles, which because of higher medication costs increases even further in patients with poor ovarian reserve, a cost-effective infertility programme has to establish criteria when a treatment cycle should be withheld because of lack of reasonable outcome expectations. This is a particularly important issue as, increasingly,

older women are pursuing infertility treatment often with almost no realistic pregnancy chance. They now, however, can be offered oocyte donation as an alternative treatment option with excellent results. To convince patients to switch from genetic to anatomic maternity can be difficult as moral and/or religious considerations can come into play. However, a cost-effective infertility programme must direct its resources away from ineffective treatments and should not support the pursuit of unrealistic treatment goals by its patients.

Level III care

Patients who reach Level III care have either failed Level II care or have, during Level I or II care, been found to be unsuitable for anything but Level III care, which involves ART. For example, if during Level I care a severe male factor is recognized, any treatment but IVF may be contraindicated. Similarly, if during either Level I or Level II care a diagnosis of severe tubal disease is reached, IVF, rather than tubal surgery, may be the only choice. As well as IVF, a number of other ART are available, though rarely applied amongst more prominent ART centres. These include gamete intra-Fallopian transfer (GIFT) or zygote intra-Fallopian transfer (ZIFT). In most large centres, neither technique is very widely utilized and IVF cycles represent the overwhelming majority of ART cycles (Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine, 1998).

Medication cost and dosage

Whether FSH-dominant products are superior to the older HMG gonadotrophins has remained controversial. Some European experiences have suggested that recombinant FSH products may be marginally better than HMG products by resulting in higher oocyte numbers retrieved and possibly lower dosages of medication (Bergh *et al.*, 1997). These data remain, however, to be confirmed in view of contradictory data (Westengaard *et al.*, 1996). Cost data in combination with outcome data seem urgently needed since the newer recombinant FSH products are significantly more costly than older, urinary-derived gonadotrophins. As noted earlier, our own, still preliminary, data suggest no advantage to the use of either urinary or recombinant FSH products over urinary HMG (N.Gleicher, unpublished data).

As has also been discussed in conjunction with routine ovulation induction, increasing medication dosages increases ovarian response only up to a certain point. Our own experience suggests that patients who require stimulation with more than six ampoules per day (450 IU) have a dismally low pregnancy rate with IVF (J.Rinehart, unpublished data).

Treatment length

The literature suggests that treatment efficacy for IVF is stable for up to four cycles, though some investigators have noted a decline even amongst those first four cycles. Our own experience demonstrates a very clear decline in pregnancy rate, basically starting after second cycles (D.Pratt and N.Gleicher, unpublished observations). Templeton and co-workers (Templeton *et al.*, 1996; Templeton and Morris, 1998) came to similar conclusions. A cost-effective fertility programme should, therefore, not offer more than four ART cycles and, possibly, fewer before alternatives, e.g. oocyte donation, are addressed.

Treatment population

Whether a woman in physiological menopause who wishes to conceive is truly 'infertile' remains open to discussion. A 25 year old with premature menopause obviously is. A cost-effective infertility treatment algorithm can, however, only be defined if the limits of treatment availability are defined.

For example, should women in physiological menopause be eligible for 'infertility' treatment or does their treatment represent a more elective treatment option, akin to cosmetic surgery? Does a woman with elevated day 3 FSH concentrations, obviously reflective of a dismal pregnancy chance, have the right to insist on an IVF attempt even if her chances are close to nil? Should a cost-effective infertility programme have the right to refuse such treatment when an alternative option of oocyte donation is being offered?

These and similar questions are as much legal (discrimination) as societal (ethical) issues which still await resolution. A cost-effective infertility programme has, however, to address such issues because limited resources should not be wasted in ineffective care.

Multiple births

Through the transfer of a limited number of embryos, IVF now allows for an acceptable level of risk of multiple births (Templeton *et al.*, 1996; Templeton and Morris, 1998). Recent Scandinavian attempts of transferring only a single embryo, point towards an evolving policy of keeping multiple births to an absolute minimum (Vilksa *et al.*, 1999). Fewer multiple births have an obvious impact on treatment costs.

Alternative ART procedures

In contrast to IVF, GIFT and ZIFT require an additional surgical procedure, a laparoscopy. Since neither GIFT nor ZIFT have been shown to offer clinical advantages over IVF, they do not seem to represent cost-effective alternatives to IVF. They may, however, be indicated in selected cases.

Due to their religious beliefs, some patients are unwilling to go through IVF but accept the option of GIFT. Whether a religious belief should be the basis for the choice of a more costly procedure is obviously a controversial issue. The recent introduction of office-based laparoscopy may allow for a more cost-conscious approach towards GIFT as well as ZIFT and may thus allow for a more liberal integration of these procedures into a cost-effective treatment algorithm.

Conclusions

Cost-effective infertility care requires a constant re-examination of practice patterns and an ongoing process of practice re-engineering. Both cannot take place unless the providers of care are fully cognisant of their outcomes in all aspects of infertility care.

We have previously proposed that infertility providers not only be judged by the outcomes in their respective ART programmes, as is currently the case through outcome reporting to a national data-bank, but by how quickly how many patients conceive after their initial presentation and at what expense (Gleicher *et al.*, 199a). Furthermore, providers should be judged based not only on

the cost to achieve pregnancy but also on the cost to have a healthy mother and child.

Considering the relatively simple treatment end-points of infertility care, it seems surprising that no effort is underway to standardize outcome and cost reporting in such a fashion. A truly cost-effective treatment algorithm for infertility care will come about only once outcome and cost reporting have been standardized.

As the world recognized that the resources applied to healthcare cannot be unlimited, cost-effective healthcare has become the new paradigm of the end of the 20th century and beginning of the 21st. Cost-effective healthcare thus has come to represent a universal goal for patients as well as practitioners, independent of nationality, insurance model and local, demographic conditions. Wherever medicine is practised, the limited availability of resources mandates their judicious use. Cost-effective healthcare is, therefore, good care and good-quality healthcare in any market can be nothing other than cost-effective care.

As clinical care evolves, cost-effective care has to evolve in parallel. The concept of cost-effective care can, therefore, never be understood as a static model; to the contrary, cost-effective care, by definition, mandates the ongoing re-engineering of healthcare and, thus, dictates a continuously maintained search for ever-improving delivery systems.

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