

Failures (with some successes) of assisted reproduction and gamete donation programs

ESHRE Capri Workshop Group*†

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BACKGROUND: Although the possibilities for the treatment of infertility have been improved tremendously, not every couple will be treated successfully.

METHODS: Crude overall pregnancy rates of 50–65% per patient can be achieved nowadays, irrespective of the type of proinfertility treatment applied first.

RESULTS: IVF only accounts for about 20% of the pregnancies achieved. Dropout is an important reason for not reaching the estimated pregnancy rate. Even after failed IVF, spontaneous pregnancies do occur. Sperm and oocyte donation (OD) offer additional chances to subfertile couples. Severity of the male factor (in sperm donation) and young donor age (in OD) are important determinants of success.

CONCLUSIONS: Analysis of assisted reproduction technology outcomes would benefit from more universally accepted definitions and deserves better statistical analysis. Long-term cumulative live birth rates of 80% may be expected if dropout can be limited. Milder stimulation, a patient-friendlier approach and better counseling may help to keep more patients in the program.

Key words: assisted reproduction technology / ICSI / intrauterine insemination / IVF / oocyte donation

† The list of The ESHRE Capri Workshop Group participants is given in the Appendix.

Introduction

What is infertility? There is no definition that can be applied universally (Gurunath *et al.*, 2011). The perception of infertility differs from one individual couple to another. It is certainly different as seen by demographers, epidemiologists and individual doctors offering treatment to those who seek help.

The Oxford English Dictionary defines 'infertile' as 'not able to have babies or produce young', which implies a state of sterility rather than 'difficulty in conceiving' or subfertility—that represents the view of many clinicians. It is hardly surprising, therefore, that much of the literature surrounding the management of subfertility is confusing and lacks clear definition as to whose perspective success or failure is being judged.

Normal fertility was defined by the European Society of Human Reproduction and Embryology (ESHRE) Group as achieving a pregnancy within 2 years by regular coital exposure (ESHRE Capri Workshop Group, 1996). Similarly, the recent World Health Organization definition of infertility is 'a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse' (Zegers-Hochschild *et al.*, 2009).

Infertile are those couples who do not achieve a pregnancy within 2 years, and they include the sterile members of the population, for whom there is no possibility of natural pregnancy, and the remainder who are subfertile. The term sterile may refer to either the male or the female, whereas the term subfertile refers to the couple. Fecundability is the probability of achieving a pregnancy, and fecundity is the ability to achieve a live birth from one cycle's exposure to the risk of pregnancy (ESHRE Capri Workshop Group, 1996).

What is success or failure? The words apply to a very wide range of activities and events. With regard to infertility and specifically assisted reproduction technology (ART), doctors and their medical team, the couple and the offspring may have differing perspectives. The variation in reported results reflects these differing perspectives and emphasizes the potentially misleading effect of publishing league tables of unedited results of individual clinics (<http://www.ivfpredict.com>).

Few would disagree that the optimal objective of ART is the birth of a single healthy baby (Land and Evers, 2004) and that elective single embryo transfer (SET) is a realistic goal (Sullivan *et al.*, 2012). But, opinions differ as to what risks (maternal and fetal) are justified to achieve this ideal. Several new outcome measures for ART have been proposed to encourage the transfer of fewer embryos, to diminish the number of multiple pregnancies and, hence, decrease the fetal risk. The implementation of these recommendations, however, is hampered by the perception that safety and efficacy are strictly connected, and it is presumed that by decreasing the number of embryos transferred, pregnancy rates will decrease as well. Data from national and international registries, however, do not confirm the assumption of the strict connection: pregnancy rates tend to be low in countries in which many embryos are transferred, and the highest pregnancy rates occur, where the number of embryos per transfer is low (Land and Evers, 2004). Conflicting interests inevitably arise and some have even called aiming for SET an 'irrational attraction' (Gleicher, 2013). The wishes of the mother to achieve a pregnancy as quickly as possible (preferably in a single cycle of treatment) may seem to conflict with the interest of the individual baby whose survival

and health may be compromised by, for example, the risk of prematurity in case of a multiple pregnancy (Sullivan *et al.*, 2012). Moreover, the overall interests of society must be considered particularly, where the costs of treatment, pregnancy, neonatal care and subsequent upbringing of the child are a responsibility of the state. Yet, we are very reluctant not to assist couples who wish to reproduce, in spite of the fact that their children are at increased genetic risk of serious life-threatening diseases. Nevertheless, through genetic counseling, the possible options to prevent disease transmission should be discussed especially within the context of ART.

Methods

Judging success

Spontaneous pregnancies occur in a proportion of women who are on the waiting list for ART, or after a previous IVF pregnancy (Pinborg *et al.*, 2009; Garrido *et al.*, 2012). Factors that may influence whether a particular treatment is successful include: the spontaneous pregnancy rate without treatment, the duration of infertility and the age of the mother (ESHRE Capri Workshop, 2005). With each embryo having an implantation potential, the chances of achieving a pregnancy rise with the number of embryos transferred. It has been suggested that the criteria of success should be expanded to include the number of single healthy live babies born within a given period of time (Heijnen *et al.*, 2004, 2007; Min *et al.*, 2004; Eijkemans *et al.*, 2006). Such an approach may include the pregnancies resulting from a given full IVF cycle (transfer of fresh and subsequent transfer of frozen embryos obtained from the same oocyte harvest, a concept developed in the recent years in the context of SET), or alternatively from successive IVF cycles. Thus, a relatively low pregnancy rate per cycle (as for natural cycle IVF) can be overcome by assessing the cumulative success rates from subsequent IVF cycles. A consensus still has to be reached on how to define success in ART in such a way that a valid comparison, between different IVF approaches, different centers or between countries, can be made. The statistical problems of such comparisons are not to be underestimated.

On the present state of statistical evaluation in ART

Statistical evaluation is a procedure that attempts to identify true systematic effects in the presence of random variations.

Although the standard of statistical competence in the research area of ART is not very high, it is certainly not alone in that regard among the biological disciplines. The main reason one suspects is that biologists usually have not studied either statistics or mathematics to any high level so that they often have to rely on anecdotal advice from others, or employ statistical packages, when in need of statistical evaluation. Often, this approach will prove perfectly adequate, but not, alas, on every occasion. A perusal of papers published in ART journals soon reveals examples of poor statistical work that has not been identified by either editors or referees. The purpose of this note is to highlight a few statistical matters that seem to be most susceptible to misuse and abuse.

Meta-analysis

Because this technique has so often been misused and the findings misinterpreted, perhaps the time may now be right to modify the entire strategy. The technique of meta-analysis aims to combine the results from several studies to produce a composite finding, for example on the effect of a treatment. If there is no evidence of study heterogeneity, the current policy is to adopt what is called a 'fixed effects' model, where

the within study error may be employed to make inferences. If there is evidence of study heterogeneity, the (generally) larger between study variation needs to be used.

Now for investigations containing relatively few studies, the test for heterogeneity will be fairly insensitive so that the fixed effects model to compare the treatments will often be adopted, by default as it were, and inferences will thus be overbold.

Under these circumstances, one could argue that the best strategy would be to summarize the effect of the treatments by the adoption of both fixed and random effect models: the publication of both types of inference will avoid the confusion that seems to exist about selecting the most appropriate model.

Some further observations on the conduct of meta-analyses in ART may be found in [Walters \(2000\)](#), [Walters \(2001\)](#) and [Walters \(2002\)](#).

Negative inference

The term negative inference may be used to describe a situation, where the analyst makes decisions based on the absence of a statistically significant result by some test. However, if the test is fairly insensitive, that is with low power, the result may have little value. To attach credence to the inference, the power of the test needs to be quoted for plausible experimental situations.

Research workers in ART need to give careful thought to the real value attached to a failure to detect a statistically significant result.

Hierarchical (nested) structures

The handling of hierarchical (nested) data structures usually poses severe problems for the inexperienced analyst who often can do no more than collapse the strata to provide a single sample of observations. If 200 data values are available on a single patient, the situation is clearly very different from the situation, where 20 observations are observed on 10 patients, despite there being 200 data values in both cases. Only in the latter case it is possible to divide the total variation into 'between patient' and 'within patient'. The situation becomes more complicated still, if there are further strata, for example 'between country' and 'between center within country'. Collapsing the strata into the lowest level, perhaps 'between patient', is a dangerous procedure as far as inference is concerned ([Walters and Edwards, 2004](#)). Unfortunately, inexperienced analysts will often proceed in that way because they are unable to cope with the nested structure and expert assistance will be needed.

The three statistical topics described above have been selected because they seem to represent the most frequent misuse of statistics in ART research. There are numerous other important matters to consider of course, but researchers would be well advised to consider carefully these few important issues when analyzing data and preparing their manuscripts.

Many of the commonly used statistical techniques assume a carefully designed study, with these properties often being impossible to achieve in ART. It is so very important, therefore, that ART researchers adopt the most stringent and rigorous attitude in those matters that are within their power.

Results

Long-term outcome for the couples

The increased need for fertility clinics

Because of the graying of Western society, the demand for infertility care is on the increase. One in 10 couples, more than ever before, visit fertility specialist clinics ([Beurskens et al., 1995](#); [De Graaff et al., 2011](#)), and their average age increases still. In The Netherlands, as a

representative of such a developed society, the mean age at first delivery increased over a period of c.20 years, from 26.5 years in 1985 to 29.4 years in 2008, a 2.9 years of increase at the moment of giving birth for the first time ([CBS Population Statistics Netherlands, 2012](#)). In the same period, the age of the female partner of couples visiting a fertility clinic for the first time increased from 27.7 [95% confidence interval (CI) 26.9–28.5] years to 31.4 (95% CI 30.6–32.2) years, making the average delay between conceiving for the first time (and delivering 9 months later) and failing to do so (and seeking medical help) 2.2 years + 9 months, i.e. 3 years ([De Graaff et al., 2011](#)). This delay brings the average age uncomfortably close to the mean age at which female fertility is going to decline. Putting the standardized demand for fertility care, i.e. the ratio between the number of women seeking fertility care and the number of women seeking pregnancy care, at 1.0 for the reference age group of 25 years, this increases to 2.5 at the age of 35 years and to 6.5 at the age of 40 years ([De Graaff et al., 2011](#)): in other words, older couples demand fertility care over six times more frequently than younger ones. This demographic shift has turned age into one of the strongest determinants of the outcome of fertility care in the early 2000s.

The long-term outcome for couples visiting a fertility clinic for the first time

A study of 946 consecutive couples approaching a modern, fully equipped fertility clinic in the early 2000s has been published recently ([Donckers et al., 2011](#)) (Fig. 1).

It has always been the practice of patient-oriented clinics to deliver individualized care, tailored to the need of a particular couple. Independently developed prediction rules for the chance of spontaneous pregnancy were applied when deciding whether to include a couple into the program for fertility workup ([Snick et al., 1997](#); [Hunault et al., 2004](#)). Couples with an estimated chance of a spontaneous pregnancy leading to a live birth of 40% or more in the next year are encouraged to continue aiming for a spontaneous pregnancy, without medical assistance, for at least another year. Couples with

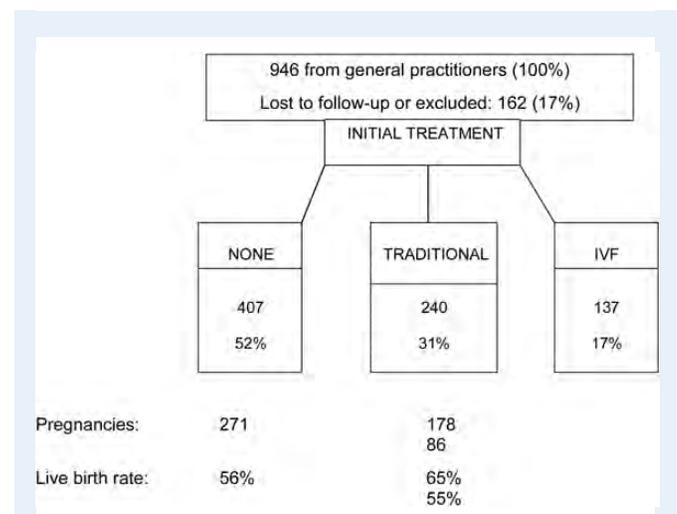


Figure 1 Patients flow chart in the study of assisted reproduction (adapted from [Donckers et al., 2011](#)).

an estimated prognosis of <30% are counseled to proceed to full fertility workup and targeted treatment. At estimates between 30 and 40%, the decision how to proceed is left to the couple's and their clinician's discretion and adapted to the individual needs and preferences. In the study by *Donckers et al. (2011)*, the number of couples who were initially counseled not to pursue active treatment immediately was 407 (52%). In this group, 271 spontaneous pregnancies occurred, leading to 228 live births (56%) and 240 couples (31%) received traditional treatment [ovulation induction (OI), intrauterine insemination (IUI), tubal surgery and cervical hostility treatment]. Of these, 178 achieved a pregnancy and 155 a live birth (65%). One hundred and thirty-seven couples (17%) were introduced directly from their fertility workup into the IVF program for either IVF or ICSI. Of these, 86 achieved a pregnancy and 75 a live birth (55%). Fertility workup showed 33% of couples to have male factor infertility as their single most important diagnosis, 23% ovulatory disturbances, 14% unexplained infertility and 9% tubal factor infertility. After appropriate treatment, the crude pregnancy and live birth rates (LBRs), respectively, were 44 and 38% in male factor infertility, 69 and 61% in ovulatory disturbances, 63 and 53% in unexplained infertility and 35 and 29% in tubal factor infertility (*Donckers et al., 2011*). IVF was the most successful treatment in the tubal factor group ($n = 65$): of the 23 pregnancies in this group, 15 (65%) were achieved by IVF, 4 following tubal surgery and 4 occurred spontaneously. In male factor infertility ($n = 240$), ICSI was most successful, with 62 of 106 pregnancies (58%), followed by 18 spontaneous pregnancies, 10 after artificial insemination donor and 7 following IUI with mild ovarian stimulation (IUI/MOS). Overall, with 263 pregnancies and 223 live births (LBR 50%) in 447 couples who received this treatment, 'no treatment' was the alternative with most pregnancies in the long run (couples counseled for expectant management, couples conceiving spontaneously in between treatments, couples without treatment due to a very poor prognosis estimate and couples conceiving spontaneously after dropping out). IVF came second, with 101 pregnancies, and 86 live births in 170 couples (LBR 51%), IUI, with 59 pregnancies and 51 live births in 118 couples (45%) was followed by OI, with 59 pregnancies and 53 live births (33%) in 163 couples.

Of 946 couples initially seen in the clinic, 162 (17%) were lost to follow-up or excluded (*Donckers et al., 2011*). Thirty-five out of one hundred and sixty-five (21%) couples dropped out after intake, but before the diagnostic workup was started, 23 out of 165 (14%) after a diagnosis had been made, but before treatment was started and 107 out of 165 (65%) after treatment was started, but before closure of the episode. Couples with female obesity ($BMI > 30 \text{ kg/m}^2$) did drop out significantly more often than others ($P < 0.0002$). Of the total group of 165 couples dropping out, 43 (26%) turned out at the follow-up contact to have conceived spontaneously within 8 years after dropping out, 59 (36%) mentioned that they had closed the episode of infertility without pregnancy and had found other ways of leading a rewarding life, 10 dropouts still considered their infertility case 'open', although they did not pursue treatment actively any longer and 53 out of 165 (32%) dropouts were lost to follow-up (5.6% of the total group of 946 couples initially attending the fertility clinic). Chances of eventually achieving a pregnancy and live birth are usually high for couples undergoing infertility treatment. However, in reality, many couples do not commence

these potentially effective therapies, or alternatively discontinue treatment prematurely.

Discontinuation is usually defined as the decision of the couple to refrain from (further) treatment; the reasons for discontinuation may not be treatment related and the couple may have a favorable prognosis. Cumulative success rates of any repetitive intervention are reduced under those circumstances due to less exposure to the benefit of subsequent treatment cycles. Improved access to treatment along with more couples undergoing repetitive treatment cycles by reducing dropouts is fundamental in augmenting overall success rates of infertility treatment.

Dropouts before treatment

A comprehensive study involving a cohort of 319 consecutive couples demonstrated that 50% of couples already stopped before any infertility treatment was initiated (*Brandes et al., 2009*) (Fig. 2). Reasons for dropping out (such as emotional distress, rejection of treatment and relationship problems) may vary and depend on many factors such as timing of discontinuation and cultural and financial situation.

Shift from assessing pregnancy rates per cycle toward integrated outcomes per started treatment

So far, IVF registries (such as Society for Assisted Reproductive Technology/American Society for Reproductive Medicine, Centers for Disease Control, ESHRE, International Committee Monitoring Assisted Reproductive Technologies and IFFS) all report outcomes per cycle. Dropouts are not considered in such overviews, and, therefore, reported results should be interpreted with great caution. It has been proposed to move away from the per cycle outcome paradigm and define a successful IVF program by the term LBR per started IVF treatment (which may involve multiple cycles) rather than per cycle (*Heijnen et al., 2004*). In medicine, outcomes of interventions are often assessed over a period of time such as success of surgery, chemotherapy or antibiotic treatments.

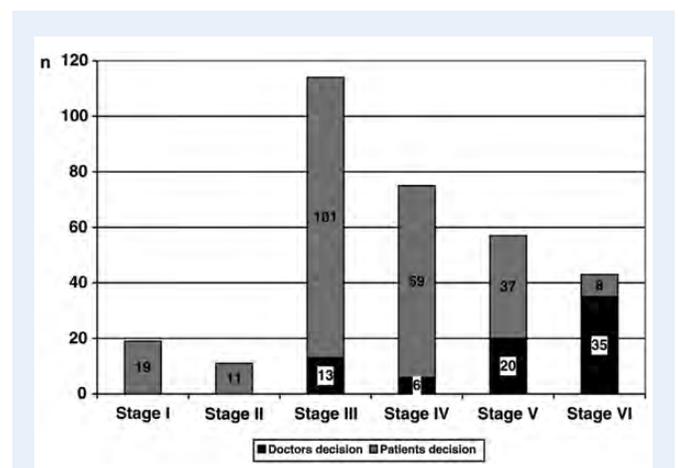


Figure 2 Summary of stages during fertility workup or treatment (total $n = 319$), where patients discontinue (*Brandes et al., 2009*). Stage I, before fertility workup. Stage II, during workup. Stage III, after workup. Stage IV, during or after conventional fertility treatment. Stage V, before third IVF cycle. Stage VI, stopped after finishing minimal three IVF or ICSI cycles.

Table 1 Factors contributing to the decision to stop fertility treatment (adapted from Boivin *et al.*, 2012).

Patient (couple)	Clinic (environment)	Treatment
Fear and negative treatment attitude	Suboptimal organization Stressful care Insufficient information Depersonalization Lack of continuity of care Bureaucratic procedures	Physical burden Physical burden Injections Cycle monitoring Work disruption Worry about cost
Psychological and emotional factors Psychological profile Difficulty in tolerating negative emotions for extended time Uncertainty Strain of repeated treatment	Negative staff–patient interaction Lack of empathy Poor listening skills Insufficient time	Handling poor prognosis Loss of hope
Relational strain Asymmetry in treatment focus		

In infertility, such figures more accurately represent the actual proportion of couples who do conceive, identifying centers with high dropout rates (Boivin *et al.*, 2012) and consequently low cumulative outcomes. Moreover, such outcomes should be considered in a more holistic context of burden of treatment, risks of complications and costs (Heijnen *et al.*, 2007). Only such an approach would encourage the development of more patient-friendly and low cost treatments.

The case of OI in polycystic ovary syndrome is a clear example of how treatments that are relatively ineffective per cycle may provide very satisfactory overall cumulative pregnancy rates (CPR) when multiple cycles are considered. A true (realistic) cumulative singleton LBR of almost 80% has repeatedly been reported, following OI applying clomiphene citrate as first-line treatment and FSH injections as second-line treatment in case of clomiphene resistance or failure (Veltman-Verhulst *et al.*, 2012). Such results can only be accomplished when dropout rates are low.

Slowly, the IVF community is changing attitude, and several large IVF units have only recently reported overall cumulative outcomes (Garrido *et al.*, 2011; Gnoth *et al.*, 2011; Stewart *et al.*, 2011). In fact, a study from Australia concluded that IVF effectiveness, especially in older patients (where per cycle outcomes are relatively low), can only be improved when women undergo many cycles (Stewart *et al.*, 2011). The most relevant information for the couple would be the accurate individual assessment of chances for success for a given treatment (which may involve multiple cycles, if needed), in the context of financial and emotional burden and chances for complications.

Understanding reasons underlying treatment discontinuation

Treatment discontinuation has mainly been studied in the context of IVF. Reported incidences vary from 7 to 80%, but most well-controlled studies suggest dropout rates around 25–35% (Boivin *et al.*, 2012; Gameiro *et al.*, 2012). In a cohort of almost 1000 couples undergoing IVF in Sweden, the majority of women did not complete 3 cycles of IVF (Olivius *et al.*, 2004). Apart from the achievement of a pregnancy, emotional problems, organizational problems and lack of autonomy were most frequently mentioned as the reasons for opting out. Another study from the UK involving structured questionnaires in

fewer patients also reported psychological stress as the most common reason for IVF discontinuation (Rajkhowa *et al.*, 2006). These observations from Europe were subsequently confirmed for patients undergoing IVF in the USA (Domar *et al.*, 2010), although financial burden was certainly also reported as a reason for treatment discontinuation due to high costs and frequent lack of health insurance coverage (as discussed by Gameiro *et al.*, 2012).

Integrated approach toward reducing burden of ART treatment

There are three specific burdens related to the infertility treatment (Table 1). These factors may all contribute to the decision of the patient to refrain from further treatment (Boivin *et al.*, 2012). Because psychological distress is directly related to the burden of treatment, interventions have been developed helping couples to better cope with this problem. Considering couples undergoing IVF more as guests—rather than patients—in IVF clinics could further reduce the burden of treatment. Moreover, an increasing number of clinics are focusing on rendering IVF treatment itself more patient-friendly, by developing the so-called MOS protocols, indeed resulting in reduced dropout rates (Verberg *et al.*, 2008).

Donckers *et al.* (2011) concluded from their study that in their infertility cohort with a 60% pregnancy rate, spontaneous conception occurs frequently: 28% when compared with 32% of treatment-associated pregnancies. Moreover, they also concluded that IVF, even when fully reimbursed, contributes only modestly to the overall pregnancy rate, providing 18% of all pregnancies (in 11% of couples). These findings agree with those of Brandes *et al.* (2010) who, in a comparable cohort, found that almost half of the pregnancies were conceived spontaneously and only 21.2% after IVF. In their group, IVF contributed most frequently to the ongoing pregnancy rate in patients with tubal factor (45%), endometriosis (45%) and male factor infertility (37%), whereas in couples with unexplained infertility and ovulation disorders, its contribution was understandably rather limited, with 13 and 5% of ongoing pregnancies, respectively, only.

These findings confirm not only that modern sophisticated high-tech fertility care has a lot to offer, but also that the spontaneous pregnancy chances of any given couple should always be put into the equation.

Patients tend to overestimate the capacity of ART to provide them with a pregnancy. It may be difficult to counsel a couple not to rush to IVF, but give nature (or for that matter simpler treatments) a chance instead. Especially, in the younger couple with a short duration of infertility, however, providing them with a clear explanation of their spontaneous pregnancy chances, reassurance and tender loving care certainly deserve a place.

Failed cycles in IVF

The German example

In Germany, SET is not practiced because of the strict Embryo Protection Law. Therefore, in Germany, the multiple pregnancy rate is higher in comparison to Sweden and the LBR is lower.

From a customer point of view, CPRs and cumulative LBRs (CLBRs) are much better indicators of success in IVF programs than cross-sectional figures per cycle or embryo transfer.

To achieve comparable results, a 10-year cohort study of patients undergoing their first ART cycle was recently conducted in Germany. Patients were followed until live birth or discontinuation of treatment. All IVF and ICSI cycles and cryocycles with embryos derived from frozen pronuclear stage oocytes were included (Gnoth *et al.*, 2011).

A total of 3011 women treated between 1998 and 2007 were included, and 2068 children were born; women who achieved a live birth reentered the analysis as a 'new patient'. For 3394 'patients under observation' with 8048 cycles, the CLBR was 52% after 3 cycles (the median number of cycles per patient), 72% after 6 cycles and 85% after 12 cycles. A CLBR of about 50% was achieved for patients below 40 years, after the cumulative transfer of six embryos. The mean LBR from one fresh cycle and its subsequent cryocycle(s) was 33%, similar to the natural fertility rate. Most couples with fertility problems can be treated successfully, if they continue treatment, and ART can approach natural fertility rates, even within the confinement of the German Embryo Protection Law.

The UK example

From 1991 onwards, the Human Fertilisation and Embryology Authority (HFEA) has collected data on all licensed fertility treatments in the UK. In their analysis based on 36 961 autologous IVF cycles between August 1991 and April 1994 (Templeton *et al.*, 1996), Templeton and coworkers found an overall LBR per cycle of 13.9%. LBRs were highest in women aged 25–30 years, with much lower rates in older women and younger women. Age-adjusted LBRs fell with increasing duration of infertility, but its cause had little effect on outcomes. A history of previous pregnancy and live birth was associated with higher rates of live birth, following IVF. The possibility of success decreased with each IVF treatment cycle. The authors were able to identify factors affecting the outcome of IVF treatment that can be used to assess the chances of individual couples.

Nelson and Lawlor used HFEA data from a different time period to examine the predictors of live birth in 144 018 IVF and ICSI cycles undertaken in the UK between 2003 and 2007 (Table II) (Nelson and Lawlor, 2011). The overall LBR in this cohort was 23.4% (95% CI 23.2–23.7). The odds of not having a live birth rose with increasing female age and duration of infertility, previous unsuccessful IVF treatments, use of own oocytes and unexplained infertility. In comparison

with women undergoing IVF, those who had ICSI had a higher chance of a live birth. The factors were used to derive a prediction model to estimate outcomes in individual couples with moderate discrimination and good calibration.

A reanalysis of anonymized HFEA data (<http://www.hfea.gov.uk>) on women undergoing their first fresh autologous IVF and ICSI cycle between 2000 and 2007 was undertaken to predict factors associated with treatment failure (Bhattacharya *et al.*, unpublished, 2012). Although anonymized data from the HFEA report cycles rather than outcomes in individual women, the inclusion of first cycles has ensured that the analysis is based on women rather than cycles. In contrast to previous analyses, odds of failure at different stages of an IVF cycle, such as oocyte retrieval, fertilization, embryo transfer and after establishment of pregnancy, have been estimated.

Data from 121 744 women were included in this analysis. Of these, 72 410 women received IVF and 49 334 had ICSI. Of those treated by means of IVF, 16 214 (22.4%) had a poor ovarian response (3 or fewer eggs retrieved); the corresponding number for ICSI was 4407 (8.9%). The risk of low oocyte yield was associated with increasing age. The proportions of women with three or fewer eggs were as follows: 18–34 year olds (IVF = 17%; ICSI = 5.3%), 38–39 years (IVF = 27.7%, ICSI = 14.5%) and in women aged 40–42 years (IVF = 36%, ICSI = 17.6%).

Of the 121 744 women who started a treatment cycle, 111 382 (91.5%) had at least 1 fresh egg brought together with sperm. In the IVF group ($n = 62\,249$), 4.7% women had failed fertilization, whereas the corresponding figure in the ICSI group ($n = 49\,133$) was 2.2%. Poor fertilization (<20%) occurred in 2.5% of all IVF cycles and 0.9% of ICSI cycles.

Of women who started an IVF or ICSI cycle, 22.1 and 6.8%, respectively, had no embryo transfer. In women with at least one embryo created ($n = 59\,329$ IVF cycles and $n = 48\,072$ ICSI cycles), 4.9 and 4.4% had no embryo transfer, respectively. Where at least 1 embryo was transferred, 33 853 (60.0%) women undergoing a first IVF cycle and 27 351 (59.5%) of women undergoing ICSI did not have a pregnancy.

In women who had embryo transfer following IVF, multivariable models showed the odds of failure to achieve pregnancy increased with female age, duration of infertility, no previous pregnancy, low number of oocytes retrieved and transfer of one, three or four embryos (as opposed to two). Cause of infertility was also associated with failure to achieve pregnancy. A similar model was found for women who had embryo transfer following ICSI (Table II).

Increased age, long duration of infertility and absence of a previous pregnancy are strong predictors of cycle failure in women embarking on IVF and ICSI. In women who manage to achieve embryo transfer, factors associated with failure to achieve a live birth in a fresh cycle include these and low oocyte yield, cause of infertility and replacement of either fewer or more than two embryos.

Spontaneous pregnancies before and after ART

There are only few publications in this area of reproductive medicine. Not surprisingly due to the unequal fertility potential of the different infertile couples and to the length of the different follow-ups, the rate of spontaneous pregnancy reported is quite variable. In the

Table II Factors associated with failure to achieve pregnancy in women undergoing first IVF and ICSI cycles that reached embryo transfer—data collected between 2003 and 2007 (Nelson and Lawlor, 2011).

Characteristic	IVF		P-value ^c	ICSI		P-value ^c
	Univariable odds ratio of no pregnancy ^a (95% CI) (n = 56 443 cycles with at least 1 embryo transferred)	Multivariable ^b odds ratio of no pregnancy (95% CI) (n = 50 615 included in analysis)		Univariable odds ratio of no pregnancy ^a (95% CI) (n = 46 002 cycles with at least 1 embryo transferred)	Multivariable ^b odds ratio of no pregnancy (95% CI) (n = 41, 331 cycles included in the analysis)	
Women's age			P < 0.001			P < 0.001
18–34	1.0	1.0		1.0	1.0	
35–37	1.25 (1.20, 1.30)	1.22 (1.16, 1.27)		1.24 (1.19, 1.30)	1.15 (1.10, 1.21)	
38–39	1.61 (1.52, 1.69)	1.50 (1.42, 1.60)		1.65 (1.55, 1.76)	1.52 (1.42, 1.63)	
40–42	2.67 (2.49, 2.85)	2.41 (2.24, 2.60)		2.81 (2.58, 3.05)	2.35 (2.14, 2.59)	
43–44	6.67 (5.51, 8.06)	6.11 (4.94, 7.57)		5.87 (4.67, 7.38)	4.57 (3.53, 5.89)	
45–50	10.40 (6.86, 15.78)	8.07 (5.14, 12.67)		11.14 (6.47, 19.18)	8.32 (4.60, 15.06)	
Duration			P < 0.001			P < 0.001
<1	0.59 (0.52, 0.67)	0.56 (0.49, 0.65)		0.62 (0.54, 0.72)	0.59 (0.50, 0.69)	
1–3	0.95 (0.92, 0.99)	0.89 (0.85, 0.93)		0.90 (0.86, 0.72)	0.88 (0.84, 0.92)	
4–6	1.0	1.0		1.0	1.0	
7–9	1.06 (1.0, 1.13)	1.03 (0.97, 1.10)		1.07 (1.0, 1.14)	1.05 (0.98, 1.12)	
10–12	1.10 (1.01, 1.19)	1.02 (0.94, 1.11)		1.15 (1.05, 1.25)	1.08 (0.99, 1.19)	
>12	1.27 (1.17, 1.39)	1.08 (0.98, 1.18)		1.39 (1.27, 1.52)	1.23 (1.11, 1.36)	
Cause of infertility			P < 0.001			P = 0.002
Tubal disease only	1.13 (1.08, 1.17)	1.30 (1.24, 1.36)		1.19 (1.07, 1.33)	1.28 (1.13, 1.43)	
Ovulatory only	0.95 (0.89, 1.0)	0.96 (0.90, 1.02)		1.06 (0.94, 1.21)	1.0 (0.87, 1.15)	
Male factor only	0.91 (0.85, 0.97)	0.97 (0.90, 1.04)		0.96 (0.90, 1.01)	1.04 (0.97, 1.11)	
Unexplained	1.0	1.0		1.0	1.0	
Endometriosis	0.96 (0.89, 1.03)	1.03 (0.94, 1.11)		0.91 (0.75, 1.11)	0.92 (0.75, 1.14)	
Cervical factors only	1.88 (0.84, 4.22)	1.84 (0.80, 4.23)		– ^e	– ^e	
Combination of known factors	1.03 (0.96, 1.10)	1.14 (1.06, 1.22)		0.99 (0.93, 1.07)	1.03 (0.96, 1.12)	
Previous pregnancy			P < 0.001			P < 0.001
Yes	1.0	1.0		1.0	1.0	
No	1.01 (0.98, 1.05)	1.15 (1.11, 1.20)		0.98 (0.94, 1.01)	1.15 (1.09, 1.20)	
Number of embryos transferred			P < 0.001			P < 0.001
One	2.84 (2.65, 3.04)	2.29 (2.12, 2.47)		3.03 (2.81, 3.26)	2.28 (2.09, 2.49)	
Two	1.0	1.0		1.0	1.0	
Three/four	1.56 (1.46, 1.68)	1.13 (1.05, 1.22)		1.46 (1.36, 1.57)	1.08 (1.0, 1.17)	
Number of oocytes retrieved			P < 0.001			P < 0.001
1–4 oocytes	2.33 (2.19, 2.47)	1.70 (1.59, 1.82)		2.52 (2.36, 2.70)	1.77 (1.63, 1.91)	
5–9 oocytes	1.36 (1.30, 1.41)	1.28 (1.22, 1.33)		1.39 (1.33, 1.46)	1.29 (1.23, 1.36)	
10–14 oocytes	1.0	1.0		1.0	1.0	
15–19 oocytes	0.92 (0.87, 0.97)	0.96 (0.90, 1.01)		0.90 (0.85, 0.95)	0.93 (0.87, 0.99)	
20+ oocytes	0.88 (0.82, 0.94)	0.93 (0.86, 1.0)		0.85 (0.79, 0.91)	0.89 (0.82, 0.96)	

Continued

Table II *Continued*

Characteristic	IVF		P-value ^c	ICSI		P-value ^c
	Univariable odds ratio of no pregnancy ^a (95% CI) (n = 56 443 cycles with at least 1 embryo transferred)	Multivariable ^b odds ratio of no pregnancy (95% CI) (n = 50 615 included in analysis)		Univariable odds ratio of no pregnancy ^a (95% CI) (n = 46 002 cycles with at least 1 embryo transferred)	Multivariable ^b odds ratio of no pregnancy (95% CI) (n = 41, 331 cycles included in the analysis)	
Embryo Utilization ^d			P < 0.001			P = 0.002
25%	0.78 (0.74, 0.82)	1.13 (1.06, 1.20)		0.69 (0.65, 0.73)	1.03 (0.96, 1.10)	
25–50%	0.87 (0.83, 0.91)	1.03 (0.98, 1.08)		0.85 (0.81, 0.89)	1.07 (1.02, 1.13)	
50–75%	0.79 (0.75, 0.83)	0.95 (0.90, 1.00)		0.78 (0.74, 0.82)	0.96 (0.91, 1.02)	
75–100%	1.0	1.0		1.0	1.0	

CI, confidence interval.

^aDefinition of no pregnancy: 'none' was recorded in early outcome results of patient scan at ~8 weeks. Molar, heterotopic, ectopic, miscarriage and biochemical recorded as achieving pregnancy (or positive pregnancy test).^bMultivariable odds ratio is adjusted for all variables listed.^cP-values were obtained from multivariable model. All covariates are categorical, and no test for linear trend was applied.^dEmbryo utilization is defined as (number of embryos transferred + number of embryos frozen)/total number of embryos created.^eThree women receiving ICSI with cause of infertility recorded as cervical factors only were excluded from the logistic regression analysis due to empty cells.

prospective cohort study of van Dongen *et al.* (2010): among the 674 women on waiting list for IUI, only 32 conceived spontaneously, mostly in the first 3 months. Donckers *et al.* (2011, p. 10) reported on spontaneous pregnancies in couples: 4 in a group of 65 tubal factor patients and 18 among 240 male infertility couples.

Spontaneous pregnancies and deliveries have been reported also in couples already treated with IVF. According to a recent publication, out of 109 couples who achieved a first live birth after IVF, 102 continued their efforts for a natural conception and 22 of them (21%) achieved a spontaneous live birth (Lande *et al.*, 2012). In a retrospective cohort study carried out in 8 centers with a questionnaire mailed to 2134 couples 7–9 years after IVF, a spontaneous pregnancy rate of 17% (218 out of 1320) has been found in couples who achieved pregnancy with ART and 24% (193 out of 814) in the couples unsuccessfully treated (Troude *et al.*, 2012). Also after ICSI treatment, a similar trend has been noted.

Between July 1992 and December 1993, 200 Belgian couples younger than 37 years of age underwent 433 consecutive unsuccessful ICSI cycles with freshly ejaculated sperm and eventually discontinued their treatment. Twenty-three deliveries were observed (Osmanagaoglu *et al.*, 2002). The cumulative delivery rate reached a plateau of 10% after 36 months of follow-up.

Sperm donation: rate of ineffective treatments

Failure of sperm donation may be assessed at various levels. Indeed, the number of recipients who did not achieve a pregnancy may be measured, but this information, in general, is not available. Most often, the pregnancy and delivery rates are reported per treatment cycle and depend upon the method of insemination used, on the age of the recipient woman (Schwartz and Mayaux, 1982; De Brucker *et al.*, 2009), on her body weight (Zaadstra *et al.*, 1993) and on the semen parameters (Freour *et al.*, 2009; Hu *et al.*, 2011).

Table III CECOS Paris-Cochin study: outcomes associated with first treatment cycles (unpublished data).

	ICI	IUI	IVF	ICSI
Couples (n)	547	1427	84	49
Treatment cycles (n)	1986	4020	135	88
Pregnancy rate (%)	6.0	14.9	27.2	26.1
Delivery rate (%)	4.8	12.1	16.3	16.8
Multiple delivery (%)	6.3	15.0	27.3	11.7

ICI, intracervical insemination; IUI, intrauterine insemination.

Sperm donation for partners of azoospermic men

Before the advent of ICSI, this was the only pro-fertility treatment available for women with azoospermic partners.

CECOS has organized in France one of the first and successful sperm donation programs.

Between 1998 and 2007, 2757 couples who requested treatment with donor sperm were included in the CECOS Paris-Cochin study (unpublished data). The women were 32.6 ± 4.3 years old, and the mean (\pm SD) men's age was 36.0 ± 6.0 years. The indication for heterologous insemination was azoospermia in 69% and other sperm defects in 27% of the couples. CECOS collected sperm from the donors and prepared, stored and distributed the individual doses to French gynecologists working in specialized centers or in private practice. They independently carried out the insemination using their own method (Schwartz and Mayaux, 1982). Clinical data were collected and analyzed by CECOS Central Office.

The first treatment was intracervical insemination (ICI) for 26% of the couples, IUI for 68%, IVF for 4% and ICSI for 2% of the couples (Table III).

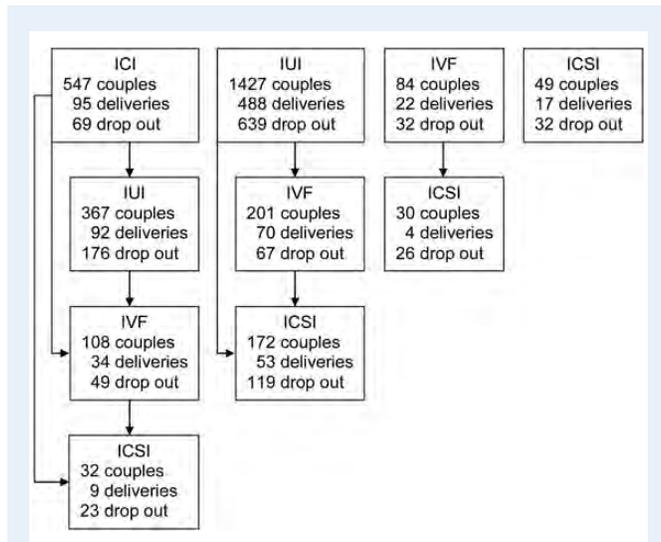


Figure 3 Donor sperm ART: treatments, deliveries and dropouts registered during the CECOS Paris-Cochin study (unpublished data).

The outcomes associated with the various ARTs are reported in Table III, and whereas the lowest delivery rate is associated with ICI (4.8%), the highest multiple pregnancy rate is associated with IVF (27.3%).

Figure 3 reports the sequence of ART used before the end of 2011 by the 2107 couples who started the program and the dropouts after each treatment. As a consequence of the heterologous insemination, 884 couples (42%) had at least 1 child: more failures (56 versus 40%) were observed with no azoospermic partner suggesting in the couple a coexisting cause of female subfertility. The effectiveness of the different treatments can be grossly compared looking at the success rate of the various techniques used at first treatment. IUI with a 15% twinning rate per cycle seems an interesting compromise taking into account that IUI cycles with MOS can reduce consistently the twinning rate (Crosignani and Somigliana, 2007). In fact, IUI is cheaper, less invasive and can be repeated each month for several consecutive months with a mean delivery rate per cycle of 13.8% (de Mouzon *et al.*, 2012).

New indications for sperm donation

The wide use of ICSI has decreased the indication for sperm donation, whereas new reproductive choices indicate the existence of new clients (Viloria *et al.*, 2011). The four main reasons for sperm donation cycles today are

- at least three failed ICSI cycles with partner's sperm,
- non-obstructive azoospermia confirmed at testicular sperm extraction,
- the social request of single women seeking conception and
- women in a female–female relationship (which is comparable to single women).

Also, the recent series report an elevated success rate: more than 25% per cycle with IUI and more that 40% per cycle with IVF. Not surprisingly, due to the higher mean age, more failures occur in the single woman group (Viloria *et al.*, 2011), as shown in Table IV.

Table IV Pregnancy rates (%) associated with the first treatment cycle in 2934 women asking for sperm donation^a (Viloria *et al.*, 2011).

Treatment and cycles (n)	Non-obstructive azoospermia (1009)	Indications ^b ICSI failure (1104)	Single women (749)
IUI 1663	29.1	27.6	22.6
IVF 1271	42.1	48.7	38.2

^aThe publication does not report the rate of twins.

^bThe few cycles carried out to avoid sexually transmitted disease are not reported.

Table V OD cycles: effect of recipient's age on pregnancy, implantation and miscarriage rate (adapted from Soares *et al.*, 2005).

	Age (years)	
	<45	≥45
Number of cycles	2683	406
Mean donor age ^a	26.0 ± 4.3	25.5 ± 4.2
Pregnancy rate (%)	49.8	44.4*
Implantation rate (%)	20.7	16.8**
Miscarriage rate (%)	16.8	23.2***
Mean number of replaced embryos ^a	2.8 ± 0.7	2.8 ± 0.7

^aNot significant.

*P = 0.045.

**P = 0.02.

***P = 0.03.

Unsuccessful outcomes in oocyte donation (OD)

The systematically delayed motherhood in many developed societies has resulted in an increased age-associated infertility rate and in a more frequent demand for donated oocytes (de Mouzon *et al.*, 2010).

A high success rate is associated with the oocyte donation (OD) due to the selection of young donors and to the multiple embryos transfer policy practiced in many ART centers (Wang *et al.*, 2012).

Garrido *et al.* (2012), looking at the efficacy of the strategy in more than 15 000 donation cycles, found that the LBR increases according to the total number of embryos replaced. Cumulative LBRs rise steadily up to 64.8% with five embryos simultaneously replaced, and the clinical pregnancy rate per cycle in many well-known centers is ~50%. Nevertheless, because multiple pregnancy is a potential risk for both the mother and for the newborn, there is a general tendency to reduce the number of transferred embryos, preferably to one, as in regular IVF (Budak *et al.*, 2007).

In a donation cycle, endometrial growth is artificially induced, and the elevated implantation rate is the best indication of the optimal endometrial receptivity. Nevertheless, some clinical data support a negative influence of uterine aging on implantation. Lack of implantation and early miscarriages were in fact more frequently found in women over 45 years of age (Soares *et al.*, 2005) (Table V).

Because it is not easy finding young donors, many infertility centers support the so-called oocyte sharing policy, a program offering to young infertile patients the possibility to donate some of their oocytes, mostly to compensate for the costs of an ART cycle. Apparently, the quality of those eggs is similar to that obtained in programs based on altruistic donors (Oyesanya *et al.*, 2009).

In older women, a pregnancy originating from a donated oocyte is also associated with an increased risk of complications during gestation and post-partum. Of special concern is the high incidence of pregnancy-induced hypertension (Pecks *et al.*, 2011; Le Ray *et al.*, 2012).

In patients with Turner's syndrome, pregnancy after OD is associated with a 2% risk of death from aortic dissection or heart rupture during pregnancy or post-partum that constitutes a 100–200-fold increase (Practice Committee of the American Society for Reproductive Medicine, 2012).

Conclusions

Key messages

- (1) The objective of (assisted) reproduction is the birth of a single healthy baby.
- (2) The desire of a couple to conceive as quickly as possible the number of children they want conflicts with the interest of the baby whose survival and health may be compromised by, for example, the risks of prematurity associated with multiple pregnancy.
- (3) ART registries should stop reporting treatment outcome per cycle and report the cumulative LBR per couple starting the treatment.
- (4) Dropouts are not considered in ART outcomes per cycle; therefore, these reports should be interpreted with caution when counseling new couples with infertility.
- (5) Human reproduction is strictly linked to trying time; therefore, mother's age and duration of infertility are the main prognostic factors, whereas repetitive treatment cycles and reducing dropout are fundamental in augmenting overall success rates of profertility programs.
- (6) Because the success rate is time dependent, many chance-related biases may influence the experimental data. Unfortunately, statistical analysis in this area has so often been used incorrectly, allowing findings to be misinterpreted.
- (7) A spontaneous pregnancy is the most frequent outcome for couples attending a fertility clinic.
- (8) Information to be provided to couples contemplating ART should include—apart from an estimate of their spontaneous pregnancy chance—an accurate assessment of their individual chance of success for a given treatment (which may involve multiple cycles), its physical and psychological burden, its costs, its side effects and its complications.

Next steps

- Analysis of ART outcomes would benefit from more universally accepted definitions and deserves the application of better statistical analysis methods by professionals who are skilled in methodology issues.

- Milder stimulation regimens, more patient-friendly approaches and better counseling may help to keep more patients in the profertility programs.
- Long-term cumulative LBRs of 80% after effective types of ART treatment may be expected, if dropout can be limited.

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Authors' roles

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Conflict of interest

None declared.

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Appendix

A meeting was organized by ESHRE (29–30 August 2012) to discuss the above subjects. The contributors included: D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), S. Bhattacharya (Division of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen, Aberdeen Maternity Hospital, UK), P. Devroey (Centre for Reproductive Medicine, Universitair Ziekenhuis Vrije Universiteit Brussel, Belgium), K. Diedrich (Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany), J.L.H. Evers (Department Of Obstetrics Gynaecology, Maastricht University Medical Centre, Maastricht, The Netherlands), B.C.J.M. Fauser (Department of Reproductive Medicine and Gynaecology, University Medical Center, Utrecht, The Netherlands), P. Jouannet (University Paris Descartes, CECOS Hôpital

Cochin, Paris, France), A. Pellicer (Presidente IVI—Catedrático de Obstetricia y Ginecología, Instituto Universitario IVI, Universidad de Valencia, Spain) and E. Walters (Thorpes, The Grip, Linton, Cambridge, UK). The discussants included: P.G. Crosignani (Scientific Direction, IRCCS Ca' Granda Foundation, Maggiore Policlinico Hospital, Milano, Italy), L. Fraser (Reproduction and Rhythms Group, School of Biomedical and Health Sciences, King's College London, London, UK), J.P.M. Geraedts (Head Department of Genetics and Cell Biology, University Maastricht, The Netherlands), L. Gianaroli (SISMER, Reproductive Medicine Unit, Bologna, Italy), A. Glasier (Centre for Reproductive Biology, University of Edinburgh, UK), I. Liebaers (Centre for Medical Genetics, Universitair Ziekenhuis Brussel, Belgium), A. Sunde (Department of Obstetrics and Gynaecology, University of Trondheim, Norway), J.S. Tapanainen (University of Oulu, Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland), B. Tarlatzis (Unit for Human Reproduction, First Dept of OB/GYN, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece), A. Van Steirteghem (Centre for Reproductive Medicine, Universitair Ziekenhuis Vrije Universiteit Brussel, Belgium) and A. Veiga (Director, CMRB Barcelona Stem Cell Bank, Barcelona, Spain). The report was prepared by P.G. Crosignani and J.L.H. Evers.