

ART data from ESHRE and the CDC show higher live birth rates in the USA than in Europe. Simon Brown asks if there really is such a big difference between the two continents - and why it might be so.

A world apart?

IVF in Europe and the USA

If statistics don't lie, the USA does IVF better than Europe. The latest American data reported from the Centers for Disease Control (CDC) show that in 2005 37.3% of all started IVF cycles in women under the age of 35 resulted in a live birth. In women aged 35-37 years the proportion was 29.5%, in those 38-40 years 19.7% and in those over 40 years 10.6%. By contrast, Europe's latest published data - for 2003 - compiled by ESHRE's European IVF Monitoring (EIM) Consortium showed an overall 'clinical pregnancy rate per aspiration' of 26.1% for IVF and 26.5% for ICSI. While the EIM described treatment cycle numbers in terms of age distribution, unlike the CDC it provided no outcome data in terms of age. Comparison, as Shakespeare wrote, may be 'odorous', but using these two data sets to draw any accurate comparative conclusions is no laughing matter.

Yet over the past few years discussion on the relative performance of the two



continents has risen from a murmur to (almost) a full-scale row. Those engaged have focused on outcome, cancelled cycles and multiple pregnancy - with an explanation for the differences implied in regulatory and funding conditions. Three years ago, for example, a report presented to the ASRM's annual meeting in Montreal by ICMART comparing worldwide IVF results in 2000 with those of the USA found higher pregnancy and delivery rates in the USA for both IVF and ICSI - but also a higher number of embryos transferred and a higher rate of multiple pregnancy.¹ The investigators attributed the higher multiple pregnancy rate in the USA to the number of embryos transferred.

The following year, 2006, the New York gynaecologist Norbert Gleicher and colleagues from the Center for Human Reproduction in New York reviewed US and European ART data for 2001 and once again found higher clinical pregnancy and live birth rates per started cycle in the USA (32.8% vs 24.3%; 27.0% vs 17.4%, both statistically significant differences).² Rates per retrieval and transfer were also calculated, and showed similar differences, as did outcome in frozen and oocyte donation cycles.

However, Gleicher ruffled a few European feathers in his contention that, 'although European patients had a significantly higher chance of reaching oocyte retrieval (ie, a significantly lower risk of cycle cancellation before retrieval), once retrieval was reached all further outcome parameters deteriorated to the disadvantage of European patients'. Gleicher added by way of explanation that 'these findings suggest that Europe is more hesitant to cancel ART cycles than the US'.

Nevertheless, Gleicher's preferred explanation for the discrepancies lay in the different contexts in which ART is performed on the two continents. Restrictive legislation, he noted, proposing the model of Italy as an example, would inevitably have 'a



NORBERT GLEICHER: 'YOU CAN'T DO YOUR BEST FOR AN INDIVIDUAL PATIENT WHEN GOVERNMENTS ARE APPLYING UNIVERSAL LEGISLATION.'

negative effect' on ART outcomes - and he seemed at a loss to understand why there was so much vocal support for regulatory intervention in Europe. Thus, in his final analysis it was the 'diverging regulatory environments on both sides of the Atlantic' which were singled out as the main driver of such imbalanced pregnancy rates, 'which do not appear to benefit the European population'. When the reaction came - as it inevitably would - it was on this very word 'benefit' that the discussion would be built. To the Europeans of ESHRE's EIM Consortium the 'benefit' of treatment lay not just in efficacy but in lower costs (including postnatal) and lower rates of multiples.³

Gleicher, who was born in Austria but has spent his working life in the

USA, remains insistent that legislation is the foremost reason for the lower outcome rates in Europe. 'It's a major point,' he told *Focus on Reproduction*. 'There's a difference in how we view what our patients want, what they're entitled to. In the US we strongly consider the wishes of our patients, and their first wish is to be pregnant. In Europe I see a much more paternalistic approach. I see in my European colleagues an acceptance that governments are entitled to tell their patients what's best for them. But to do the best for our patients we need to practise on an individual basis, to individualise treatment. The US system caters for that approach, but the European system does not. You can't do your best for an individual patient when governments are applying universal legislation.'

In 2007 Gleicher was back in print with an updated comparison - now based on 2002 data - and a mission to see if the divergent trends of 2001

The USA and the rest of the world in 2000

	Worldwide	USA
Aspirations	367,731	63,861
Pregnancy rate		
IVF	26.7%	38.5%
ICSI	27.7%	35.2%
Delivery rate		
IVF	18.6%	31.0%
ICSI	20.4%	28.6%
Mean number of embryos transferred		
IVF	2.5	3.0
ICSI	2.7	3.1
Twin pregnancies	27%	31%

ALAN COPPERMAN: 'PATIENT-FRIENDLY IVF MUST BE ASSOCIATED WITH A HEALTHY NEWBORN ACHIEVED IN A SAFE, COST-EFFECTIVE, AND TIMELY MANNER,'



were moving even further apart.⁴ Lower pregnancy rates in Europe, Gleicher now reported, 'remain of concern', but he offered no further explanation other than to discount the larger number of embryos transferred in the USA and to reaffirm the negative impact of a rigid regulatory environment in Europe. However, Gleicher also raised the caveat that Europe's 'aggressive recent efforts' with single embryo transfer would also have a negative impact on 'already very low pregnancy and exceedingly high ART usage rates'.

Europe's response to such utilitarian US arguments has depended largely on quality (if not quantity) and a belief that the 'benefit' of an ART cycle lies not just in a basic pregnancy rate but more - as Nick Macklon proposed in last September's *Focus on Reproduction* - in the birth of a healthy (singleton) baby delivered at minimum cost and at minimum risk and discomfort. One assumes that such a belief similarly lies behind the acceptance in Nordic countries of single embryo transfer, or today's growing interest - especially in Europe - in 'modified' natural cycle IVF, 'soft' IVF, and 'patient-friendly' IVF.

Patient-friendly IVF

Yet patient-friendly IVF, argue the Americans, is not the sole prerogative of Europe - once again, it depends on how it's defined. In September last year three specialists from Reproductive Medicine Associates in New York and New Jersey (Flisser, Scott and Copperman) took up the

issue and argued that to define patient-friendly IVF as synonymous with minimal stimulation IVF was based not on 'tried and true protocols' but on 'a dearth of evidence-based, peer-reviewed data'.⁵ For them, genuine patient-friendly IVF lies not in the mumbo-jumbo of minimalist strategies but in the clinics which have 'responded to patient needs with sensitivity by trying to make infertility treatments more palatable'. For example, says Alan Copperman, therapists in US clinics are now routinely available for patients with emotional needs, computerisation has increased the efficiency of treatment scheduling, and satellite offices of central laboratories have made treatment more accessible. But he also notes that these advances have not been identified by the public as making IVF more patient-friendly. That term has instead been hijacked by the 'practitioners of minimalist IVF'; this spin-doctoring, argues Copperman, inherently prejudices patients against other forms of treatment and, by implication, suggests that all alternatives are 'unfriendly'.

Indeed, most (but not all) American commentators - as current guidelines from the ASRM would suggest - have no doubts that the ideal of treatment is the birth of a healthy singleton baby. 'Patient-friendly IVF must be

associated with a healthy newborn achieved in a safe, cost-effective, and timely manner,' says Copperman; and even Gleicher, who cannot yet accept the preferability of singletons over twins, accepts that 'it is satisfying to note that both continents are moving towards smaller embryo transfer numbers'.

Even at the more formal level the latest CDC surveillance of American ART (for 2004) has described the contribution of ART to preterm births in the USA as 'a key concern'.⁶ The CDC's report found that 50% of infants born through ART in 2004 were multiples, compared with 3% in the general US population. The twin rate was 44% (15 times higher than in the general US population), and triplets 6% (42 times higher). Multiple rates were highest in those using fresh embryos from their own eggs (53%) or from donor eggs (60%). As a result, the CDC urged 'implementation of approaches to limit the number of embryos transferred for patients undergoing ART' and to view treatment success in terms of singleton pregnancies and births.

ASRM guidelines

Such a concern is also implied in the ASRM's guidelines on embryo transfer, which were updated for a third time in 2006.⁷ However, the ASRM somewhat coyly described 'high-order' multiple pregnancies as three or more implanted embryos, and ignored any comment on twins. The ASRM also rejected any notion of 'strict limitation' (as evident in some European legislation) as a restriction on individualised treatment plans. Thus, as the box on the next page indicates, the ASRM proposed a sliding scale of recommendations which ranges from just one blastocyst in younger patients with a good prognosis to five embryos in women over 40.

While many in Europe would be sympathetic to the ASRM's sliding scale, the prevailing European view -

The latest ASRM guidelines on embryo transfer

	Age <35	Age 35-37	Age 38-40	Age >40
Cleavage-stage embryos				
Favorable prognosis	1-2	2	3	5
All others	2	3	4	5
Blastocysts				
Favorable prognosis	1	2	2	3
All others	2	2	3	3

Last year a report from SART (Society for Assisted Reproductive Technology) found that implementation of the ASRM's embryo transfer guidelines was associated with significant reductions in the number of embryos being transferred, along with reductions of high order multiple pregnancies.⁸ While plotting a decline in the number of embryos transferred (four or more, though not three) the SART investigators were able to show that the most dramatic rates of change were between 1997 and 1998, the year immediately after the January 1998 publication of the original guidelines, and between 1998 and 1999, the first full year after publication. However, the analysis also found that twin delivery rate did not change over the same time frame.

whether regulatory or self-recommended - is that patient interests are now best served by transferring one or a maximum of two embryos. Indeed, much of the outcome discussion evident in presentations at last year's annual meeting of ESHRE was confined to single or double embryo transfer, even in older women. Three embryo transfer, as EIM data would confirm, has been virtually removed from the radar screen in most of northern and western Europe.

Single embryo transfer

In the USA, however, the attraction of single embryo transfer - even as a concept, let alone a reality - still seems a long way away. According to the CDC, singleton live birth rates from fresh non-donor cycles increased from 17% in 1996 to 23% in 2004 - and by even more in frozen cycles.⁹ However, the same report also found that, from 1996 to 2004, the number of single embryo transfer cycles increased only 'slightly' (from 6% to 8%), while cycles involving the transfer of two embryos increased 'dramatically' (from 10% in 1996 to 39% in 2004). Cycles transferring three embryos also increased from

23% in 1996 to 32% in 2004 - although transfers of four or more embryos did decrease (from 62% in 1996 to 21% in 2004). Indeed, by 2004 the same CDC data were showing that in younger women (under 35) with several embryos available the chance of a live birth from ART was highest (53%) when two embryos were transferred.

Norbert Gleicher describes single embryo transfer as an 'ideological' and not a scientific issue, whose attraction is based on an ill-conceived mathematical model which fails to recognise the benefit of two children. Nevertheless, while Gleicher sees SET as already 'contaminating' ART in the USA, there are still several groups there showing that SET can provide acceptable outcomes within the US model of free enterprise. At the ASRM congress last year, for example, a group from Rockville, Maryland, after analysing their five-year ART records from 2002 (12,135 cycles of fresh embryo transfers), reported that SET in a large IVF programme - with 'physician, staff and patient education on the risks and benefits' - can reduce multiple pregnancies without compromise in outcome. Pregnancy

rates for elective SET were 68% in 2006 compared with 61% for two blastocyst transfers. In a separate presentation, researchers from Duke University, after estimating the cost-effectiveness of different embryo transfer strategies, also found that, while the short-term transfer of three embryos provided the lowest cost-to-delivery ratio, single embryo transfer was less expensive in the long term because of complications arising from multiple gestations.

There are those who say that comparison of two such 'inhomogeneous' ART environments as the USA and Europe is a futile exercise. But the CDC's data suggest that the USA is no less disparate or varied than Europe.⁶ There too the availability of ART services is patchy - and largely dependent on reimbursement. Uptake of ART in the USA is highest in California, New York, Massachusetts, Illinois and New Jersey, but such a ranking - as in Europe - seems more determined by insurance coverage than population size alone. Using the same model as ESHRE's EIM Consortium, the CDC found greatest availability of ART per million population in Massachusetts (1384), District of Columbia (1227), New Jersey (981), Connecticut (823), and Rhode Island (790). This picture, said the CDC, was not unexpected because in 2004 Massachusetts, New Jersey and Rhode Island all had statewide mandates for insurance

FROM 1996 TO 2004, THE NUMBER OF SINGLE EMBRYO TRANSFER CYCLES IN THE USA INCREASED ONLY 'SLIGHTLY', WHILE TWO EMBRYO TRANSFERS INCREASED 'DRAMATICALLY'.

coverage for ART. EIM data presented in Lyon last year similarly showed that availability of ART in Europe seemed directly related to the funding background. Highest availability was found in Denmark (2128 per million population), where ART is almost totally reimbursed. And, just as availability varies from state to state in the USA, so the EIM found huge variability throughout the states of Europe (584 per million in Austria, 665 per million in UK, 1974 per million in Belgium, and so on). With average availability hovering around 1000 cycles per million inhabitants, the patchwork picture in Europe seems not too different from the USA.

It was in the context of states without insurance coverage that the CDC also expressed fears that patients 'might feel pressured to maximize the opportunity for live-birth delivery' and ART providers 'to transfer multiple embryos to maximize their publicly reported success rates'. In Europe in 2003 the EIM found the greatest number of embryos (four plus) transferred in Greece, Lithuania, Hungary, Bulgaria and Ukraine, all countries with (at the time) little regulation and no state funding.¹⁰ The pattern, surely, is not too dissimilar from the USA.

The US view of Europe

As ever, to find an agreed generalised view of how the USA sees ART in Europe is not easy. Norbert Gleicher acknowledges that most Americans would respect Europe's contribution to the history and innovations of ART, but would still feel that the procedures are now performed better in the USA. Mark Sauer sees Europe 'toiling' under its burden of restrictions, but still admires 'the level of honesty in Europe that you can trust' and its flexibility ('how legislation in Italy and Germany is now driving research in oocyte freezing'). Alan Copperman also agrees that most US specialists are well aware that many of the great advances in ART have come from Europe. 'But there is,' he says, 'a

Egg donation: from corner store to supermarket



Mark Sauer, left, whose clinic in Los Angeles in the early 1990s was largely responsible for the boom in oocyte donation, sees American practice in the technique today as dependent on the USA's lack of regulation. 'Back in 1990 both Europe and the USA were at the same research point in egg donation,' says Sauer, 'but they've developed in different ways. In the USA it was quickly taken into the practice sector as an opportunity for commercialisation. In Europe it's remained out of the mainstream, mainly because of regulation.'

At Sauer's own clinic at Columbia University in New York around 10% of all ART cycles are now egg donation, a proportion consistent with other major centres and one likely to increase with an ever-ageing patient population. ESHRE's EIM data for 2003 showed only 7548 oocyte donation cycles performed from an ART total of 365,103 cycles (2.07%).

There are US guidelines on egg donation, Sauer concedes, 'but it always comes back to commercialisation, meeting demand and providing access. It's not like the UK, for example, where the best practice guideline is actually governed by law.' The UK sets limits on payments to donors (only to cover expenses) and gives children conceived from donor gametes the right - at 18 years of age - to know the identity of the donor. A cycle of egg donation treatment in the big centres of the USA can cost as much as \$25,000, and donors themselves make on average \$5000 per cycle - although \$10,000 is not unknown. The escalation in payment, says Sauer, is yet another result of having no regulation.

'Egg donation is now a big industry in this country,' he adds, 'and the reason we do so much more than in Europe is simply because of commercialisation. The difference has always existed, but the practice grew and developed in a different direction because there were no regulations here - and any guidelines could easily be ignored.'

Sauer says live birth rates are now fairly constant at around 50% per transfer, but adds that the bigger centres transferring blastocysts are reaching as high as 70% per transfer.

consensus that success rates are now significantly higher in the US.' This difference, he adds, may be related to IVF usage patterns in the USA and the number of embryos transferred per patient - but possibly to stimulation protocols and laboratory techniques.

But for most Europeans - and indeed for many Americans - the salient issue in American ART remains the high rate of twin pregnancies. SART last year acknowledged that, while the ASRM guidelines have had an impact in reducing the number of embryos transferred and the rate of high order multiple pregnancies,

'much progress is still required before our goal of a healthy singleton birth for all couples is achieved'.¹¹ To actively lower the twin rate, SART continued, the majority of the US ART community would have to change its priorities from 'the best chances of pregnancy with minimal risk of high order multiples' to 'the best chance of a singleton pregnancy with no likelihood of multiple pregnancy'. To effect this change, acceptance of the advantages of exchanging lower birth rates for lower twin rates is vital, said SART, which so far has not occurred.

The impact of cumulative IVF cycles in the USA and three European countries

	Fresh cycles			Frozen cycles			Deliveries fresh (%)	Cumulative deliveries (%) (fresh + frozen)	All multiple deliveries
	Started cycles	Deliveries	Multiple deliveries	Frozen cycles	Deliveries	Multiple deliveries			
Sweden	9593	2027	115	3205	498	48	21.1%	26.3%	6.5%
Finland	4761	886	118	3434	518	55	18.6%	29.5%	12.3%
UK	30495	6747	1635	7349	1072	172	22.2%	25.6%	23.1%
USA	94242	26059	8478	18560	4658	1129	27.7%	32.6%	31.2%

A calculation for ESHRE's EIM Consortium presented in Lyon last year by Professor Anders Nyboe Andersen showed that, when the outcome of frozen cycles was added cumulatively to that of fresh cycles to give a cumulative live birth rate per started cycle, the live birth rates found in three European countries were only a little lower than those found in the USA. The variation in multiple delivery was more marked. (The calculation was based on the EIM's and CDC's data for 2004.) Nyboe Andersen, in presenting the findings in Lyon, described cumulative deliveries per started cycle as 'the optimal end-points' in ART. SART, in its comment on multiple gestations last year, identified the greater recognition of cumulative live birth rates (by both insurers and data collectors) as one step towards a higher rate of singleton deliveries in the USA.

The way forward towards a goal of singleton deliveries in the USA would depend on improved funding for research in embryo selection, an altered structure of insurance coverage (which recognises the cost implications of lower order embryo transfers and cumulative cycles), new data reporting parameters (which also recognise cumulative cycles resulting from a single egg collection - see the box above), improved patient education, and a consistent catalogue of regulation and recommendation which avoids medical tourism and links a singleton delivery target to obstetric and neonatal cost savings.

Although these are the words of SART - and related only to the practice of ART in the USA - the objectives and challenges raised are surely comparable with those heard in Europe every day. Are the two continents so much different? IVF may be more expensive in Los Angeles than in Lithuania, just as restaurants charge more in Paris, France, than in Paris, Kentucky. That's life. And just as patients from Idaho may cross state lines to find the best treatment in New York, so too they will cross borders from Italy to find the best treatments

in Spain. There may well be differences in efficacy and differences in legislation, but, as SART's outline of the challenges facing the USA suggests, there's much overlap too. And the Atlantic may not be as wide as some Americans - and Europeans - would have us believe.

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