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- Guidelines: Fertility (update): NICE guidance (*BMJ* 2013;346:f650)
- Editorial: Mental disorders in children after IVF (*BMJ* 2013;347:f5257)

Are new technologies in IVF always good news?

Couples desperate to conceive may want to try costly new techniques that they've heard about from the lay media—even if their success is unproved. **Richard Hurley** reports

When vulnerable couples trying in vitro fertilisation (IVF) learn of news reports about promising new techniques they may well demand them from their general practitioner or infertility clinics. They may be prepared to pay hundreds of pounds in the hope of improving their chances of a pregnancy. GPs and specialists too may be influenced by such coverage.

But these technologies might not actually work. The randomised controlled trials needed to show effectiveness can take years to perform. Many women near the end of their reproductive life, however, or after several unsuccessful cycles of IVF, and who are desperate for a child don't have time to wait 10-15 years to find out.

A retrospective study of one such technique was published on 9 May this year in the peer reviewed journal *Reproductive BioMedicine Online*.[1] It described use of time lapse imaging to spot embryos at high risk of genetic abnormality, a key cause of failure in implantation, or later miscarriage, in IVF. Professor Simon Fishel, part of the team whose work led to the first IVF baby and managing director of the UK's largest private infertility clinic, the Care Fertility Group, was a coauthor.

The *Times* newspaper covered the story, headed online, "New IVF technique could give 78 per cent chance of success." Fishel was quoted as saying: "In the 35 years I have been in this field, this is probably the most exciting and significant development."[2]

If true, this would indeed be exciting because it would represent a twofold or threefold increase in success rates.[3] However, Nick Macklon, professor of obstetrics and gynaecology at Southampton University and director of the Complete Fertility Centre, was less impressed. Although the technique might have promise, he wrote in a letter to the *Times*, rigorous testing for effectiveness was needed before it could be recommended.[6] "Journalistic enthusiasm for 'new breakthroughs' which ignores the lack of evidence of benefit opens infertile couples to exploitation," he wrote, accusing the *Times* of hyping the paper's message.

"This was presented as the definitive study," Macklon said at a discussion about the coverage of the story at London's City University on 25 September.

Fishel, who was also at the City University debate, thinks that it might sometimes be worth trying untested treatments if they have shown some promise and couples are short on time. "IVF was not proved by an RCT," he said.

For fear of misrepresentation of their work, the study authors had involved the public relations agency the Science Media Centre, which ran a journalists' briefing on 16 May. During this hour long session, the paper's authors described it as "the beginning of something revolutionary" and "a game changer."

"You'll agree that these are very impressive results," said Martin Johnson, editor of the journal and emeritus professor of reproductive sciences at Cambridge University. He went on to caution that all-important prospective randomised studies were needed. But this mention of the study's limitations lasted only two minutes.

"It was not the first time and it will not be the last time where a scientist does not go out of their way to emphasise the limitations," Fiona Fox, chief executive of the Science Media Centre, told the *BMJ*.

"It's an easy hit for journalists to make minor developments seem important"

The centre did, however, give journalists the written reactions of four independent experts.[7] These included, "Before we splash this on the front page it should be subject to full randomised control trials." Many news outlets quoted these experts, but the *Times* did not. It included such caveats only briefly and at the end of its story.

Problems conceiving may affect as many as one in seven UK couples.[8] Stories about fertility treatments "set the hearts of news editors racing," explained Hannah Devlin, science editor at the *Times* and who wrote the story, at the City event.

"And they come with pictures of cute babies. They're almost too easy to get into papers. It's an easy hit for journalists to make minor developments seem important," she said.

This isn't the first time that patients might have suffered for overblown stories about infertility research. More than a decade ago, preimplantation genetic screening in IVF was heralded as the answer to implantation problems, Macklon said at the City event. These hopes, built on positive initial observations and plausible biology, were dashed, however, when in 2007 the first randomised controlled trial showed that the £700 technique in fact reduced the chances of successful implantation and hence pregnancy.[9]

"While the commercial return of such stories for the clinics reporting them is strong, the evidence supporting their effectiveness is usually weak," Macklon said in his letter to the *Times*.[6]

In the UK much IVF treatment occurs in private sector clinics, which compete for market share, said Macklon on BBC Radio 4's *Woman's Hour*.[11]

"It's a scandal, but that's where we are," he said at the City debate. "The websites of clinics give only the stories they want to tell."

And do such stories hinder recruitment of patients to the very clinical trials that would provide robust evidence of effectiveness? Once patients have "been filled with PR" why would they agree to be randomised and potentially not receive the treatment, Macklon asked at the City event.

"Scientists are now under a great deal of pressure to go out and educate people about what they are doing. But if journalists don't handle the information responsibly then that is a great problem," Johnson, the journal editor, told the *BMJ*.

Doctors, scientists, and press officers must keep trying to make sure that reporting research does not cause harm to patients, the City debate concluded. But ultimately newspaper reporters, subeditors, and editors must ask them the right questions to ensure that they give their readers the truth.

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Industry fights Europe over regulation

Proposals for regulating medical devices in Europe are proving controversial, finds **Deborah Cohen**

Kafkaesque and harmful to patients are just two of the ways that new proposals to change the way medical devices are regulated in Europe have been described by industry organisations.

The planned reforms would create an "FDA-like system [that] would kill patients and kill innovative companies," says Eucomed, the European medical technology trade association.[1]

But, as previous *BMJ* investigations have shown, the current system for allowing devices on to the market leaves patients across Europe vulnerable to poorly performing products.[2] The system has led to a raft of headlines involving failed devices—including hip prostheses, intracranial stents, vaginal meshes, breast implants, and pacemakers.

Some of the 80 notified bodies—private organisations charged with evaluating the safety and reliability of devices—have been exposed as being more interested in attracting business than guarding the safety of patients. It's those bodies that give companies a certificate to allow them to display a CE mark and sell throughout Europe.[2]

It's a system that academics have described as "fragmented, privatised, and largely opaque; safety is dealt with in an unsatisfactory way and efficacy not at all."[3]

And it would seem that many members of the European Parliament (MEPs) agree. On 25 September, a committee of MEPs on the environment, public health, and food safety committee agreed a series of changes that will see far more oversight and transparency than before with extra scrutiny for the highest risk devices.

Fifty two MEPs voted in favour, 12 against, with three abstentions.

Good or bad?

But are the new proposals, which MEPs vote on later this month, a boost to patient safety or will they lead to economic demise and patient harm—the opposite of what they're intended to do? It depends who you listen to.

For some, the changes don't go far enough—they would have liked to have seen a central body assessing the safety and efficacy of high risk devices, as German socialist MEP Dagmar Roth-Beherendt initially proposed.

"I've been over 20 years in Brussels and I haven't seen such strong lobbying pressure before," she told *Der Spiegel*, the German weekly news magazine, this week.

The European Association for the Study of Diabetes (EASD) has also called for a central "European Device Agency."

They are also anxious that the insulin pumps and other equipment used to treat people with diabetes might not fall into the "highest risk" category and therefore won't have extra oversight. "We are talking here about devices that people depend on for their lives, such as insulin pumps and technology that monitors blood glucose," says Professor Andrew Boulton, the president of EASD.

HOW EUROPE WANTS TO GET TOUGH

- Special "notified bodies" will be formed to oversee the CE certification of high risk medical devices
- Notified bodies will have "in house" staff with medical, technical, and pharmacological knowledge and be able to assess or challenge evidence
- A new requirement to have a review of clinical studies by a "third party or external expert under the principles of highest scientific competence and impartiality"
- The names of those in charge of assessment and any relevant conflicts of interest will be published
- An assessment committee with groups from 21 medical and surgical specialties will scrutinise the evidence around some high risk devices. When there is concern about a particular device, it will be sent to this committee
- There will be unannounced inspections of the notified bodies
- Introduction of an open access databank called Eudamed that will log devices, including those removed from market
- Eudamed will contain certificates, details on clinical investigations, and postmarketing follow-up
- Patients harmed will be compensated for any damage and associated treatment as a result of a faulty medical device
- Devices will come with an implant card that is to be given to patients and recorded in notes

But some—including the Directorate General for Health and Consumers (DG Sanco), of the European Commission—do not like that approach.

Eucomed and the DG Sanco work closely together. At a recent launch party to celebrate the launch of new Eucomed offices, for example, representatives from DG Sanco provided an official welcoming statement.

Neven Mimica, the European Commissioner for consumer policy, told the *BMJ*: "We are happy that we have departed from the idea of a centralised body in charge of authorisation. It is felt that the current proposals strike the right balance between innovation and safety," adding: "We want to keep the edge that industry has here in Europe."

A European Commission spokesperson said: "We do not believe that we are improperly close to industry," adding: "We regularly meet with all parties to discuss the work of the commission."

That "edge" is a key argument in the debate. Even though the proposals have been watered down, Eucomed is still opposed to the changes and says that MEPs have failed to make good political promises to support European innovation and boost jobs. Europe is risking its position as a global leader in the numbers of patents filed, says a 2013 Eucomed factsheet.[4]

Eucomed surveyed its members to assess the financial impact of the proposed changes and estimated that it would cost an extra €1m-€4m (£850 000 to £3.4m; $1.4m-$5.4m) to bring a high risk device to market.[4] Some of those costs come from the requirement for more clinical evidence before manufacturers can market the products in Europe. The survey findings were drawn from responses of just 19 of a potential 25 000 device makers in Europe.[1]

Eucomed hopes that politicians will prioritise profit and employment protection. As one medical technology pundit laid bare on an industry website this month: "The world's medical device makers, small and large alike, rely on Europe's efficient decentralised approval system to launch their products in a timely manner and prove to investors that their products serve patients well and are financially viable," they wrote.[5]

Not everyone is convinced. Pierre Chirac, vice-president of *Prescrire*, the French medical journal that has argued that patients need better protec-




From left: John Bowis, of Health First Europe; European Parliament, Brussels; the PIP implant that sparked a health scandal; and *BMJ* device investigations

tion, says the same points were made to stop drug regulation being tightened.

"On the economic side, the medical device companies' arguments are very similar to those heard between the 1960s to 1980s, when pharmaceutical companies were anxious about drug approval becoming stricter," he told the *BMJ*.

Slower to get devices

Another plank of Eucomed's campaign against the proposals is called, "Don't lose the 3." Far from being guinea pigs for the US market, Europeans benefit from getting "life saving" procedures at least three years before Americans, says Eucomed. Manufacturers have to demonstrate the safety and effectiveness of many high risk devices before the US Food and Drug Administration grants market approval —something that doesn't routinely happen in Europe, as *BMJ* investigations have shown.

"I've been over 20 years in Brussels and I haven't seen such strong lobbying pressure before"

Examples cited include the transcatheter heart valve (TAVI) and renal denervation to control severe hypertension—a procedure seven million Americans are waiting for, according to Eucomed.[1]

The evidence for "Don't lose the 3" comes from a June 2012 report by the Boston Consulting Group (BCG), funded by the medical technology industry.

But critics of the report say that three years is an exaggeration. They say that the latest proposals on the table are actually quite different from the FDA approach.

Not that industry agree—the *BMJ* has seen an invitation to MEPs sent by a group of industry associations this week arguing that the new proposals are like the FDA, "a pathway we always tried to get around for good reasons." It goes on to say that industry has "severe concerns" and some fears it will "shut down business."

This earlier access to lifesaving technologies does not factor in health service considerations across Europe—reimbursement or health technology appraisals that green light the use of a product. Access to market is one thing; access to a patient is another. Renal denervation, for example, has been approved in Europe since 2010 but has only been fully reimbursed in Germany and Austria as of 2013, according to healthcare analysts GlobalData.[8]

Joseph Gregory, surgical devices analyst at GlobalData, says it's the state of the clinical data that is important. "While company-sponsored studies have to date proven short-term safety and efficacy, there is still ambiguity with regards to device performance in the long term, as well as the degree of efficacy that can be achieved," he said in a press release this month.[8]

So, although devices seem to get approval far quicker in Europe than in the US, there can still be many delays before they are used on patients.

Others also question if fast track access is always a good thing. As reported in the *BMJ*, widespread early adoption of the transcatheter heart valve before the trials had reported for the US market meant that the device has not always been used in the right subset of patients.[9]

Rita Redberg, a cardiologist and editor of *JAMA Internal Medicine*, has testified to Congress in the US about device regulation.

"I think we need to be more specific about 'innovation.' Most new devices are not innovative. And even if they are—unless they are life saving and there is no other treatment—I think we need clinical data to show safety and effectiveness before getting on the market and better postmarketing surveillance as well," she told the *BMJ*.

Revolving interests

It's not the first time that the BCG has produced reports for industry that support the status quo. A 2011 report analysed device recalls in both the US and Europe and found that there was little difference. "Differences between the two systems do not ultimately affect performance," it said in a press release.[10]

Quoted on the press release was John Wilkinson, then chief executive of Eucomed.

Fast forward to 2013, Wilkinson—in his role as head of medical devices at the UK's Medicine and Healthcare Products Regulatory Agency (MHRA)—describes the European proposals as "disproportionate" and says that the MHRA is uncomfortable with the ambiguous language.[11 12] The MHRA also opposed a central device agency.

A MHRA spokesperson says: "We have been clear from the outset of negotiations that it's vital that the European system of regulation is strengthened so that people are protected against unsafe medical devices," adding: "We have also been clear that any changes to the regulatory system should be proportionate and deliver real benefits for patients."

Some see this kind of positioning as an example of the fast moving revolving door between policy makers and politicians and industry that is clouding the debate.

Former MEPs and former employees of the public health arm of the European Commission are now lobbying on behalf of industry. Dario Pirovano, an Italian national who drafted earlier devices guidance when he worked at the commission, is a regulatory adviser to Eucomed.

Former Conservative MEP John Bowis is now honorary president of Health First Europe, an industry-patient alliance, and wrote on the European parliament website that reducing rapid access to medical technology "ultimately harms patients rather than protects them."

Bowis's view is that patients are willing to take on risk to progress new cures and treatments. "We want risk minimised and monitored; we do not want no risk," he said. On the parliament website, there is no mention of the fact that Health First Europe's entire 2013 funds were all from Eucomed.[13 14]

Celine Bourguignon is a former member of the commission, where she was a policy officer in the cosmetic and devices division. She is now lobbying MEPs on behalf of Cordis-Johnson and Johnson against proposals to make it more difficult to label a device as single use only.

However, despite the fierce battle for hearts and minds, Commissioner Mimica told the *BMJ*, he thought that no European countries were totally against the need for change. How this all plays out when MEPs gather later this month remains to be seen.

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