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Intracytoplasmic sperm injection: offering hope for a term pregnancy *and* a healthy child?

We need a common approach to definition and detection of birth defects

See p 1260

One of the most recent techniques of assisted reproduction, intracytoplasmic sperm injection, offers hope for those suffering from subfertility, and particularly male factor infertility. This hope is tempered by worry, since couples who undergo this procedure might never become pregnant or, if they do, may not carry the pregnancy to term. Added to these known risks are theoretical risks regarding birth defects: intracytoplasmic sperm injection involves fertility drugs, chemical baths, and physical procedures, any of which could increase malformation rates. Moreover, if left to nature, the sperm manipulated by this procedure would probably not produce a pregnancy, and these sperm themselves may carry an increased risk for birth defects.

Some reassurance about these theoretical concerns was offered recently when researchers from Belgium reported that major birth defects affected only 3.3% (14) of 423 children born after intracytoplasmic sperm injection,[1] a rate no higher than in the general population. In the current issue, however, Kurinczuk and Bower provide a less reassuring interpretation.[2] Using the classification scheme and data from the highly regarded Western Australia birth defects registry, they note that many major defects in the Belgian series had been incorrectly classified as minor. Reclassification yielded 31 major defects, or 7.38%; compared with the Western Australian rate of 3.78%, the risk of major defects following intracytoplasmic sperm injection was increased twofold.

Although the Belgian group has expanded its experience to 877 children, with an overall major malformation rate of 2.6%,[3] these later findings are based on the same analytic approach and may similarly be called into question. On the other hand, researchers from New York recently found only nine major malformations among 578 babies born after intracytoplasmic sperm injection,[4] a rate of only 1.6%—less than half that in Western Australia. Even if the six minor defects they identified were reclassified as major, the resulting rate of 2.6% is still below the expected. Do these findings suggest that birth defect risks can be minimised if couples undergo this procedure in New York rather than Belgium, or might something else explain these discrepant results?

The Western Australia researchers correctly argue that for comparisons of birth defect rates to be valid, investigators must use the same definition of what constitutes a birth defect in both the study and the comparison population. However, a common definition can only be imposed on information that is available in the first place. Whatever definition is used, no amount of reclassification can correct problems resulting from underreporting or overreporting of birth defects, and in the Belgian and New York studies we have examples of both.

The New York findings are probably explained by underreporting, since information on birth defects for 80% of the babies born after intracytoplasmic sperm injection was derived from reports offered by gynaecologists or paediatricians, an approach that, without standard and systematic examinations, cannot assure either consistency or completeness. In contrast, 76% of the babies born in the Belgian study were examined by a birth defects expert. However, examinations went further since "routine heart ultrasonography [was] done for ICSI babies born intra muros."[1] Most of the minor cardiac anomalies identified in that series were detected by this diagnostic technique, though they were transient or did not require surgery. Indeed, we suspect that few if any of these "defects" would have been identified through a systematic (and clinically meaningful) examination (a similar phenomenon has been described for other occult conditions[5]). Thus, one can reasonably surmise that the large and disproportionate numbers of cardiac malformations in the Belgian data are due to overreporting, not to intracytoplasmic sperm injection. Other specific noncardiac malformations were too few to be informative.

When detection differences and the nature and distribution of the defects noted on both sides of the Atlantic are thus taken into account, the data do not suggest that any of the many factors associated with intracytoplasmic sperm injection causes a substantial increase in the overall risk of birth defects, and that is reassuring. Unfortunately, neither do these data provide the rigor needed to rule out modest increases in risks of malformations overall or even large increases in specific defects. We should remember that human teratogens typically increase specific defects (each affecting less than 1 per 1000 livebirths), not defects overall (affecting about 3-4%),[6] and to learn about these more relevant risks requires not only rigor but large numbers.

The researchers engaged in intracytoplasmic sperm injection should be commended for their considerable efforts to study not just the benefits of the procedure but also its potential risks. Through the

European Society of Human Reproduction and Embryology they have developed a task force to assess both the efficacy and safety of various intracytoplasmic sperm injection techniques.[7] What is needed now is for the society, with appropriate epidemiological guidance, to adopt a common definition of birth defects and a common approach to detection, including how and by whom defects should be identified.

Patients and their doctors have benefited immensely from the experiences of those who preceded them, and if properly presented, the vast majority of patients undergoing intracytoplasmic sperm injection and their doctors would probably welcome the opportunity to contribute their experiences to others who follow. Medical researchers and clinicians have given many subfertile couples hope that they can bear a child. These same doctors can and should extend their efforts so that these couples can also know whether a child conceived through this means is at increased risk for birth defects.

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Conflict of interest: AAM's research group receives support from Hoechst-Marion-Roussel and he has reviewed research findings for the company on clomiphene and neural tube defects. He was also an examiner of Dr Bower's PhD thesis.

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When lifesaving treatment in children is not the answer

A set of guidelines that reflect clinical and emotional reality

> Axioms in philosophy are not axioms till they are proved upon our pulses.—John Keats

Last month the Royal College of Paediatrics and Child Health produced guidelines on the withholding or withdrawing of lifesaving treatment in children.[1] Such documents face the potential problem that in their attempt to achieve consensus the recommendations can become so vague as to say nothing. Any guidelines will find it difficult to achieve credibility in the face of the drama of a critically ill child, a drama in which the uneasy actors—parents; children; and nursing, medical, and allied health staff—so often find themselves painfully entrapped.[2] When I first read the royal college's report I thought it a brave and dignified document which nevertheless stayed polite and superficial. But, with each rereading, I realised that in fact it is a remarkable report which does indeed make the leap to the bedside. It achieves sense and clarity without losing any connection with the emotions being played out in the theatre in which I and many others work.

The report's greatest contribution is in delineating "five situations where withholding or withdrawal of curative medical treatment might be considered": the brain dead child, the permanent vegetative state, the no chance situation, the no purpose situation, and the unbearable situation.[3] The report is refreshingly and remarkably child centered, although it acknowledges the key position that parents hold. Although the general thrust of the report is similar to that of many others on this subject, such as that of the American Academy of Pediatrics,[4] the child orientation suffusing it gives it a subtly different and very acceptable emphasis.

Nevertheless, there are points to comment on. Firstly, the report perpetuates the view that, ethically, withdrawing and withholding therapy are equivalent. Theoretically this is no doubt correct, but, as the report itself confirms, that is not how it feels to either parents or staff. When most people who are actually dealing with these problems think that there is a difference between the two forms of medical action there is a strong case for revisiting the issue. Valid principles sometimes grow out of shared perceptions at the bedside.

Secondly, while the report acknowledges that withdrawing life saving treatment is not the same as withdrawing care, it nevertheless portrays palliative care as the soft option. This perpetuates the feeling that anything other than aggressive intensive care is second best. The practice of intensive care centres around the excitement of the moment, the rapid response, the spectacular success or the noble failure. Such a discourse by its nature cannot help equating withdrawal of treatment with no treatment. While the authors have been careful to address this with the addition of the words "life sustaining," the word "withdrawal" is the dominant message. Withdrawal is the active, decisive step against passive second class alternatives. But the actual choice here should be about "managing the transition from one style of care to another" and "moving from a tactical approach (focusing on each intervention) to a strategic approach (aiming at defined goals)".[5] The ability to make such a choice may not be within the training of staff, who will

then oscillate between continuing aggressive treatment and withdrawing abruptly rather than changing treatment direction.

Palliative therapy is not negative. It is overwhelmingly positive in the best traditions of medicine and nursing. It aims to provide as good a quality of life as possible, with the duration of that life becoming the second order consideration, but still important as long as the quality is maintained. Paradoxically, paediatric intensive care is sometimes the best place to start and continue palliative care. It is often the only place where team management comes together with the will and ability to look at the whole picture and apply immediate and aggressive solutions. In addition, withdrawal of life saving therapy is not an all or none phenomenon, but rather a strategy by which to test different treatments. This, although alluded to in the report, needs more emphasis to those who will have to put this into practice.

Thirdly, despite the complex issues involved, the report confirms that "it is usual in the individual case for there to be complete agreement of all concerned." Sometimes, however, there is dissent when parents demand treatment that is considered futile by the healthcare team. Our own unit in Sydney has found this a particularly difficult problem. The report discusses this briefly and agrees that "there is no obligation to give treatment which is futile and burdensome." Their solution to the problem of dissent is time, counselling, and then the courts (with no real support for the idea of ethics committees). This is a rather glib response to an extreme scenario where trust between staff and parents has broken down. It is not clear whether the authors consider that the courts would support the withdrawal of treatment in the face of parental opposition. Interestingly, the American recommendations are more wary of judicial review. Surely the ultimate solution must not lie in conflict at the bedside but in a policy discussion at government level about resource use: what society is prepared to provide and how far this can be influenced by unrestrained individual demand.

These are minor criticisms. This is an important document, which will grow in importance. I commend it for its dignity, its lucidity, and its sense of clinical and emotional reality.

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The future of preschool vision screening services in Britain

We need better research on which to base policy decisions

What should be done in Britain about existing and proposed programmes to screen preschool children for the related conditions of amblyopia, refractive error, and strabismus? Those who have visited this debate before may not be surprised that the recently published systematic review on preschool vision screening from the NHS Centre for Reviews and Dissemination identified serious deficiencies in the research evidence which informs current policy.[1] However, the conclusions that "Providers currently offering screening programmes should consider discontinuing them" and, "From an ethical point of view, it is appropriate to continue to screen only in the context of a controlled trial of treatment" will undoubtedly prove more controversial.

The available research evidence has been interpreted differently in similar reviews from North America,[2,3] where it has been concluded that preschool vision screening should continue. Why have reviewers reached different conclusions from essentially the same data? By integrating existing information in an unbiased manner, systematic reviews should provide data for rational decision making[4] and stimulate focused debate about policy and future research needs. There are, however, inherent difficulties when reviews are based largely on observational rather than experimental data, as their interpretation is likely to be less straightforward.

The main purpose of screening and surveillance for visual defects throughout childhood is the early detection and treatment of relevant ophthalmic disorders to minimise their impact on a developing child. As up to 6% of preschool children will have an ocular or vision defect requiring treatment or follow up,[1] some form of preschool vision screening service has been offered in most health districts for the past 20 years.[5] In addition, children currently receive a further examination at school entry. As the United Kingdom review has policy implications for modifying or discontinuing existing preschool services,[1] it is important that its recommendations are viewed in a broader context.

The key question for policymakers is whether a programme of preschool vision screening offers benefits over existing vision screening at the school entry examination (currently the subject of a separate review from the Centre for Reviews and Dissemination). This question probably cannot be answered definitively by reviewing systematically identified literature of the quality currently available. While ideally policy should be informed by evidence from a randomised controlled trial, further work would be required to clarify its

purpose and design as well as the most appropriate measures of outcome. The role of other quantitative methods could be explored—for example, a decision analysis to assess the effectiveness, including cost effectiveness, of differing preventive strategies, which would help determine research priorities.[6]

Perhaps the most challenging finding of the review for the ophthalmic community is the lack of evidence from trials to support the main treatments for amblyopia—namely, occlusion combined with spectacle correction as necessary.[7] As the almost universal use of these treatments in clinical practice is derived from extensive clinical and basic scientific research on stimulus deprivation amblyopia,[7 8] prospective studies of the natural history of untreated amblyopia may be difficult. However, clinical uncertainty remains about when to start and how long to continue with occlusion therapy, how to modify treatment according to the response achieved, and finally how to monitor concordance with treatment.[9]

All these issues should be addressed in any future treatment trials, which will depend critically on the involvement and collaboration of ophthalmic professionals. Another important issue is the age above which treatment of pre-existing unilateral amblyopia may not succeed. Although treatment is considered to be most effective in early childhood, there is some evidence from observational studies that improvements in acuity can occur, sometimes spontaneously, in some affected adults,[10] and this merits further exploration.

The review also identifies the need to understand better the long term functional consequences of untreated unilateral amblyopia, about which only limited information is available.[11] One component of this is being investigated through a national collaborative study of the incidence, causes, and outcomes of loss of vision in the non-amblyopic eye of individuals with pre-existing unilateral amblyopia.[12] However, there remains the important question of the disability attributable to amblyopia per se, which partly reflects the inherent difficulties of measuring and interpreting visual function in children.

The findings of this review present us with the dilemma of what to do when there is little evidence, particularly of the right sort, specifically supporting the benefits of an existing service and none proving it is ineffective or detrimental. In the current climate there is a danger that existing, but incompletely researched, services may be discontinued prematurely. The challenge raised by this review is how to secure a sounder evidence base for policymakers which reflects "clinical reality and its inherent difficulties."[13] Implementing this research agenda will require a close partnership between those concerned with planning, providing, evaluating, and using these services.

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Too soon to market

Doctors and patients need more information before drugs enter routine use

The present system by which new drugs enter the National Health Service is failing doctors and patients. It leads to prescribing and funding decisions being made on inadequate information, causes duplication of effort, and creates geographical inequities in the availability of drugs. We need a new approach which takes account of relative effectiveness and cost utility.

Drugs in Britain are licensed on the basis of the applicant's evidence of efficacy, acceptable toxicity, and proper manufacture. Much of the information on which the decision is based is unpublished at the time of licensing, although the European licensing body, the Committee for Proprietary Medicinal Products, now publishes summaries of its opinions. Doctors then have to decide whether to prescribe the (often expensive) new drug and health authorities to allow or resist its use. They turn for help to local sources of advice such as drug and therapeutics committees.

The doctors and pharmacists who provide advice at local level suffer from several handicaps. The published evidence is all they have and is usually inadequate. For example, donepezil, a recently licensed drug for Alzheimer's disease, is supported by only one randomised controlled trial published in full, with follow up of just 12 weeks.[1] This is long enough to show a treatment effect but hardly useful for routine clinical practice, where the issue is one of longer term efficacy and safety. Even practical aspects of its short term use, such as how best to monitor clinical effect or define treatment failure, have not been adequately addressed.[2]

Sometimes the evidence of benefit from new drugs seems flimsy. Riluzole, licensed recently for use in amyotrophic lateral sclerosis (a form of motor neurone disease), clearly has some efficacy, but because this is at best modest and the drug has no effect on muscle function,[3] its role in treatment is uncertain.[4] The unpublished data seen by the licensing authorities have not been scrutinised by the scientific community and may not have been peer reviewed, which limit their suitability for use in prescribing and funding decisions. The same concerns also apply to their use in licensing decisions.

Prescribers and prescribing policymakers increasingly want to take cost utility into account, but no analyses are available when a decision is required. Local groups have limited resources and expertise for appraising the information that is available, and their efforts are duplicated in other hospitals and health districts. In any case, local groups' decisions are often merely advisory. Their advice to resist or restrict use of a drug may be overwhelmed by the manufacturer's marketing efforts and the lobbying of patient groups. In this way, the limited money for growth in the NHS is spent on some of the least understood and proved remedies.

One pernicious result of this system is further loss of geographical equity. As different districts reach divergent conclusions about expensive drugs, patients find that whether they receive treatment depends more on their postcode than their disease, their wishes, or their doctor's advice. This confuses patients, corrodes public confidence in the integrity of the NHS, and is irrational and unnecessary. Regional bodies have emerged to advise on interventions of uncertain benefit.[5] These have helped but still duplicate effort (four have examined donepezil) and can promote inequity and confusion if their conclusions differ and lack mandatory force.

Although the current licensing hurdles may establish a drug's efficacy and safety, they are not enough to earn it a place in an evidence based healthcare system. Prescribers need to know how this drug compares with other available therapeutic options, and prescribers, policymakers, and funding agencies need to calibrate the health benefit yielded by a new drug against other ways of tackling the same or another health problem. Yet trials of comparative efficacy and economic analyses are not part of the licensing process, so the results of such studies are delayed or never available.

What can be done? We need another hurdle which a drug must clear before its routine use in the NHS is permitted. An independent body should test a drug's value with two questions: Is the drug sufficiently well researched, especially its relative effectiveness? Is its cost utility acceptable? Limited prescribing in evaluations designed to answer these questions would be allowed but nothing more.[6] The clinical experience accumulated in post-licensing evaluations would enable clinical guidelines to be prepared before general release, in consultation with patient groups. Only then would drugs be available for general prescription in the NHS. If these measures were adopted local and regional assessment would be redundant.

A similar system operates already in Australia,[7] a country with a less influential indigenous pharmaceutical industry. In Britain ministers are said to be considering setting up a new committee to decide whether new drugs and other treatments are sufficiently cost effective and well proved to be available through the NHS. That would be a powerful way for the Department of Health to match its exhortations about improving clinical and cost effectiveness in prescribing with real action.

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Opiate detoxification under anaesthesia

Enthusiasm must be tempered with caution and scientific scrutiny

At least 10 000 opiate misuers have recently undergone a new detoxification treatment in which acute provocation of withdrawal by opiate antagonists is administered under the cover of a general anaesthetic.[1-3] This technique has been variously hailed as a revolutionary breakthrough or condemned as exploitation of the addicts and their families. While neither the antagonist provocation nor the use of a general anaesthetic is new the combination has apparently captured the imagination of some clinicians, misuers and their families, and commercial interests—the treatment is available only in the private sector and is expensive.

Much of the controversy has been generated by competing claims of effectiveness and competence from rival providers. Anyone trying to make an objective assessment has been hampered by the lack of information about techniques and of any independent evaluation.[3] Indeed, the starting position should be that this technique needs to be shown to produce clear cut benefits sufficient to offset its inherent dangers.[4] These include both the hazards of prolonged general

anaesthesia and those that must result from the sudden pharmacological bombardment with an opiate antagonist—as well as adrenergic agonists, antiemetics, and antidiarrhoeal agents.

The "new" detoxification procedure has a history dating back a century to attempts to achieve painless detoxification under general anaesthesia. This was followed in the 1960s and 1970s by the use of deep narcosis. In practice, the anaesthetic is unlikely to provide anything more than a means of bypassing the distress of withdrawal, though that will contribute to the acceptability of the procedure.

The development of antagonist-precipitated rapid detoxification has a separate ancestry. Since the early 1970s attempts have been made to use naloxone (without an anaesthetic but sometimes with deep sedation) to achieve more rapid detoxification.[5-8] Injections of naloxone provoke an immediate severe withdrawal response, but this severity seems to decrease steadily as the doses of naloxone are repeated. Within 48 hours further injections of naloxone no longer provoke substantial withdrawal symptoms. Protocols for a combination of clonidine and naltrexone were developed during the 1980s.[9 10] These paved the way for studies by Loimer in Vienna in the late 1980s using general anaesthesia to cover the carefully monitored use of naloxone to precipitate detoxification[11-13]—techniques which form the basis for the methods used today by others.

This new technique seems to have two potential advantages which warrant careful consideration. Firstly, misusers fear detoxification[14] and may be more willing to undergo detoxification if they can avoid the acute withdrawal discomfort traditionally associated with it and perhaps also the longer term symptoms of fatigue, dysthymia, and poor sleep.[15] Assessment of these outcomes must, however, be rigorous enough to identify which benefits are truly associated with the technique and which are a Hawthorne effect associated with the novelty and mystery of the new procedure. Secondly, the new procedure is said to lead to better completion rates. Plainly, a procedure which anaesthetises the patient will have high completion rates, but the crucial question is whether this benefit carries through to stable abstinence. Greatly improved long term abstinence rates may be due to selection bias, with patients with a good prognosis being the ones willing to seek and pay for the treatment. Another factor might be the supervised treatment with naltrexone after detoxification.

Any assessment of the claims made for the procedure will need to include the possible disadvantages—which seem likely to be substantially greater than with existing standard detoxification methods. As well as the hazards of prolonged general anaesthesia, high doses of naloxone or naltrexone may occasionally lead to life threatening adverse reactions.[16] These hazards might be expected to be even greater if anaesthetic detoxification were attempted in existing drug treatment programmes, whose staff lack the training and experience to care for patients during anaesthetic and recovery periods. Life threatening atypical reactions[4] and several deaths have now been reported during, or immediately after, such procedures. Mortality and morbidity will presumably be likely to be even greater among patients with concurrent dependence on alcohol or benzodiazepines or liver disease. More generally, the apparent simplicity of this new detoxification method may lead to misusers, their families, and their carers failing to appreciate the longer term nature of the problem. Finally, the reported ease of detoxification could even lead to unexpected adverse effects such as possible increased initiation into heroin use.

New detoxification methods which have important and unavoidable hazards should not be made widely available until reliable data are available from controlled studies. Addiction causes such major distress to patients, family, and carers that they will understandably search for new treatments which promise great benefit without risk. The medical and scientific communities have a responsibility to ensure that any new procedures are described accurately and that rigorous studies are made of the benefits and hazards. The lack of such information about anaesthetic detoxification remains disappointing, prevents rational decision making about the justifiability of this new approach, and is a damning indictment of the medical and scientific communities so far. Until there is adequate evidence of effectiveness and safety for this technique it should be used only in clinical trials.

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Correction

Attention deficit hyperactivity disorder

An editorial error occurred in this editorial by Florence Levy (1997;315:894). In reference 7 the journal should have been *Journal of Child Psychology and Psychiatry*, and not *Archives of General Psychiatry*.