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As Sure As Eggs? Responses to an Ethical Question Posed by Abramov, Elchalal, and Schenker

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INTRODUCTION

In September 1999 a group of Israeli *in vitro* fertilization (IVF) researchers (Yoram Abramov, MD, Uriel Elchalal, MD, and Joseph G. Schenker, MD) published a debate article in the journal *Human Reproduction* questioning the ethics of using high doses of ovulation stimulation drugs for fertility treatment.¹ The article, “Severe OHSS: An ‘Epidemic’ of Severe OHSS: A Price We Have To Pay?” considered the widespread aim of obtaining high numbers of eggs in assisted reproductive technology (ART) treatment regimes in relation to the commercial goal of fertility clinics to establish a reputation for high rates of success. The authors proposed that these institutional and commercial goals might expose patients to an increased risk of the severe form of the most common iatrogenic complication of fertility treatments, ovarian hyperstimulation syndrome (OHSS). Using statistics on the side-effects of fertility drugs, the authors provided a new collection of long-term data from Israeli clinics to support their claims. The article suggested that rates of OHSS could be understood by reference to the increased use of high-yield drug regimens and the widening use of ART. In aligning the ethics of decisions made at the clinical level with a broader question about the aims of ART practitioners, they challenged their colleagues to reappraise the legitimacy of the current high levels of drug stimulation. In essence, the authors were posing a cultural question in a clinical context.

This kind of reflective approach is unusual in ART literature,² and the present study proposes that an analysis of the responses to the article by Abramov and colleagues provides an opportunity to examine the ethical culture in which ART is practiced. Since the article by Abramov and colleagues was unusual in arguing for a cultural shift, it seems timely, after around seven years, to follow up its reception in the literature. How was it received? Did it convince colleagues? I will propose that, by analyzing the responses — or indeed the absence of responses — to this article, it may be possible to trace, at least partially, an “ethical profile” of current ART practice. Beyond this, I will address a more general cultural question: What happens when, from the midst of a professional group, someone challenges some of the cherished assumptions of that group?

Bioethical writing about ART has tended to ignore the persistent reporting of dangerous complications from the routine use of fertility drugs, and ethical debate is, with some exceptions,³ largely preoccupied with issues of rights: of egg donors and embryos, for example.⁴ These debates tend to rehearse vexed ethical

questions, often with public policy in mind, but by and large they do not address the clinical realities of ART. I will therefore seek, as a third aim, to contribute to a broader understanding of what constitutes a bioethical inquiry.

This is not a philosophical study: I am a cultural historian, and this article is primarily a qualitative analysis. Lest the impression be given that saying something is "qualitative" is simply a way of justifying bias, I should make clear that this research arises from a concern for the welfare of women suffering OHSS during fertility treatment. There is a vast sub-literature on OHSS within reproductive technology reporting, most of which has historically concerned the refinement of clinical protocols that aim to either diminish or forestall the syndrome. However, it is rarely suggested that one way to diminish the incidence of OHSS would be to practice restraint in the administration of fertility drugs. Yet this is what Abramov, Elchalal, and Schenker did. Such an argument naturally runs hard up against the view that patient autonomy is the gold standard for judging clinical ethical practice, and that doctors who worry about the effects of their drugs might be seen in this light as being paternalistic. However, unless the practice of medicine is to be regarded as no different from that of technicians in auto repair, I suggest that there is, and should be, room for doctors' concerns about patients' safety to be set alongside nostrums about autonomy that simplify a complex clinical and ethical scenario.

APPROACH AND METHODS

I will begin by describing the findings and ethical claims of Abramov, Elchalal, and Schenker. Then I will describe how many published studies in subsequent IVF research did not cite their article, and how many did, through April 2006. I will consider the basis for citing the article: whether it was to endorse the authors' views directly, challenge them, or for another reason. Further, I will suggest that, in all the articles examined, the language and argumentation, as well as some of the clinical scenarios described, provide an insight into clinicians' and researchers' ways of thinking about OHSS. Because I did not know what to expect when I began this inquiry, I have built my categories of analysis around the material as I found it. Inevitably this approach has been informed by the priorities that I brought to the study; I argue nonetheless that anyone making an analysis on the basis of ethical concerns about women's health might come up with similar results. To that extent, the nature of the inquiry makes the exercise repeatable.

BACKGROUND: OHSS

Most fertility treatments use drugs to stimulate a female client's ovaries to make them produce more than the usual single monthly egg. In IVF, egg and sperm are combined in the laboratory to form an embryo or embryos. Women who will be inseminated *in utero* are also generally given fertility drugs to increase the number of mature ova in their bodies prior to insemination. All fertility drug protocols involve a degree of hyperstimulation of the ovaries.⁵ While most of the drugs that are administered as part of medical treatment are intended to return the body to normal and stable functioning, fertility drugs are an intentional intervention designed to induce an abnormal response. However, the relative difficulty of precisely controlling ovarian response to fertility drugs, combined with a widespread view that maximizing the number of ova per treatment cycle is the most desirable outcome of a treatment, has led to the regular occurrence of ovarian hyperstimulation syndrome (OHSS). Minimizing cost has also been identified as a factor.⁶ The "underlying [physiological] mechanism" for OHSS is "capillary hyperpermeability mediated by ovarian-derived vasoactive substances."⁷ In leading the body to create perhaps 10, 20, or even 50 times the mature egg follicles it usually does,⁸ fertility drugs introduce a hormonal imbalance that can result in morbidity and the risk of mortality. A predisposition among certain IVF clients to conditions such as polycystic ovary syndrome has made it possible to identify some clients who are at a higher than normal risk; however, there is no single indication for OHSS other than the drugs themselves.

Three categories of OHSS have been determined by clinicians: mild, moderate, and severe. Estimates

vary widely as to the incidence of OHSS in all its forms, but it has been stated that up to 10 percent of all cycles result in some form of OHSS.⁹ Severe forms (0.2 to 1.0 percent) often require hospitalization to avert potentially lethal effects, and many patients with moderate cases of OHSS are also hospitalized.¹⁰ Fauser and colleagues reported in 1999 that at least 5,000 women per year worldwide suffered serious OHSS.¹¹

The biological changes that characterize severe OHSS have been described as "profound systemic vascular dysfunction, with increased vascular permeability, loss of fluid into the third space and intravascular dehydration."¹² This can produce "massive ovarian enlargement, ascites, pleural effusion, oliguria, haemoconcentration and thromboembolic phenomena."¹³ In lay terms, OHSS appears to arise as a result of the overstimulation by exogenous (externally administered) hormones of those endogenous (naturally occurring) ovarian hormones that affect the ways in which fluids circulate in the body. The ovaries swell and blood vessels and other means of containment of fluid become permeable; fluids seep into inappropriate passages, and necessary fluids fail to follow their normal paths, which can lead, for example, to an incapacity to urinate, blood clots (including stroke), fluid in the abdomen or lungs, or liver or kidney failure. Depending on the intensity of the toxic effect, patients experience symptoms including abdominal distension, pain, nausea, vomiting, diarrhea, and inability to breathe.¹⁴

A notable rise in the incidence of OHSS has occurred since the mid-1980s in the wake of the introduction of complex drug protocols, involving the suppression of the normal ovulatory cycle and re-stimulation of the ovaries. Deployment of a series of drugs, usually by daily injection over a period of weeks, has tended to supersede the use of drugs such as clomiphene citrate, the "fertility drug" of the 1960s and 1970s. The more common procedure, increasingly favored in IVF since the mid-to-late 1980s, is to introduce so-called GnRH analogs, which act to suppress the normal pituitary stimulation of the ovaries and hence suppress natural ovulation. This "false menopause," sometimes preceded by administration of contraceptives, requires the subsequent use of drugs such as human menopausal gonadotrophin (hMG): a blend of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), or FSH alone, to induce the production of multiple egg follicles. Once eggs approach maturity, clients are generally administered with human chorionic gonadotrophin (hCG) to stimulate the final maturation and the release of eggs from their follicles.¹⁵ The use of this protocol makes control of a woman's ovulation easier, making it less likely that a treatment cycle would need to be cancelled. The rise in OHSS appears to be a consequence of increased numbers of egg follicles developing following the use of high doses of hMG/FSH, and thence an increase in the number of mature follicles that respond to the added stimulation of hCG.

There is no dispute in the literature that OHSS is iatrogenic.¹⁶ Debate revolves, however, around whether a large number of eggs should be the main criterion for clinical success, or whether lower numbers of eggs might provide an equal likelihood of successful pregnancy.¹⁷ A further tension seems to lie in the choice by many clinics to obtain a large number of eggs that can be frozen as embryos and retained for later use by a client if the initial round of treatment fails.¹⁸ While certain categories of clients are at greater risk of OHSS, reduced doses of hMG/FSH and hCG can nonetheless contribute decisively to reduced rates of the condition across the board.¹⁹ The problem lies in the tension between competing clinical goals.

THE CASE MADE BY ABRAMOV, ELCHALAL, AND SCHENKER: CLINICAL FINDINGS AND ETHICAL CLAIMS

Abramov, Elchalal, and Schenker examined the period 1987 to 1996 in 16 out of 19 tertiary care facilities in Israel, and considered the medical records of all patients hospitalized for severe OHSS. They found that 78 percent of the patients "were undergoing IVF, while the rest received conventional ovulation induction treatments."²⁰ The remaining 22 percent appeared to include cycles of egg donation, not only induction of non-IVF ovulation; 94 percent of those with severe OHSS who received IVF had undergone pituitary suppression followed by exogenous gonadotrophins. In total, 2,902 patients were hospitalized for moderate OHSS and 209 for severe OHSS. In other words, of 73,492 cycles of IVF performed in the survey period, around one in 25 resulted in the client's hospitalization for OHSS in some form, and 2.8 per 1,000 clients, or

slightly more than one in 500, led to hospitalization for severe OHSS. The authors do not mention the possibility that severe cases may have been treated without admission to a hospital, but this would have been an unusual scenario, given that more than 10 times the number of severe cases were admitted to a hospital for only moderate OHSS.

For the period in question, the authors noted a six-fold increase in the use of IVF to treat infertility alongside a 20-fold increase in the incidence of severe OHSS. They related this increased likelihood of a client contracting severe OHSS to "a more liberal use of ovulation induction medications."²¹ In turn, they identified "the over-utilization of high-dose gonadotrophin protocols" with increasing competition between fertility clinics, and argued that "oocyte and embryo numbers [were] considered as main (*sic*) criteria for . . . success."²² They identified this development with the increased use of cryopreservation and possibly with expanded egg donation programs, in which numbers are an intrinsic aspect of "success," largely separable from the pregnancy outcome of the clients. (That is to say, a "successful" round of egg donation might result in 20 or more pregnancies, none of them necessarily in the donor.) They concluded by setting out their ethical challenge: "we should ask ourselves how far we are willing to go in treating infertility, and where we should draw the line so that life is not endangered."²³ The authors rejected as questionable two often-cited prophylactic interventions, intravenous albumin and "coasting" or withholding administration of gonadotrophins, and urged "revision of the eligibility criteria for extracorporeal fertilization treatments as well as serious reconsideration of the currently used ovulation induction regimens."²⁴ This last proposal regarding eligibility criteria appeared to refer to IVF clients who were most physiologically vulnerable to OHSS, or perhaps to egg donors who constituted a growing client class — or to both.

The authors' emphasis was on the possibility of restraint in the administration of drugs and on limiting the number of clients. They deliberately asserted a direct connection between clinical practice and commercial priorities, to challenge the ethical thinking of their colleagues. I determined what I see as the article's distinctive ethical thrust, on the basis of its title, posed as a question to colleagues, and on the explicit challenge to consider the possibility of losing the "competitive edge" by reconsidering who is treated and with what level of pharmaceutical intensity. The article can, in that way, be distinguished from the majority of OHSS-related literature, which, while concerned with patient care, generally assumed that OHSS is a given in routine IVF. That is, most of the literature on OHSS appeared to be produced in the context of discussion of its occurrence, rather than focusing on the instance of its occurrence. The analysis here of responses to and citations of Abramov, Elchalal, and Schenker takes its cue from the authors' own emphasis. Thus, even the articles that considered patient care, but neither addressed directly the ethical concern raised by the authors, nor appeared to examine the ethics behind the levels of intervention they described, I will treat as having ignored the primary aim of the article by Abramov and colleagues.

CITATIONS AND RESPONSES

An internet search using the Thomson Scientific ISI Web of Knowledge cited reference search on "Abramov, y*"; 1999, on 9 April 2006, yielded 21 references, plus two that were bibliographically defective (one gave an incorrect page reference for the original article²⁵ and another is referred to as "in press" for *Human Reproduction* 1999, even though this article appeared immediately following Abramov, Elchalal, and Schenker, in the same issue²⁶). For the purpose of comparison, it is noteworthy that a U.S. Library of Medicine PubMed search for "ovarian hyperstimulation syndrome" for the period September 1999 to April 2006 yielded 681 references. If Abramov, Elchalal, and Schenker can be regarded as equivalent to the declaration of a state of emergency in the field, the number of articles that are traceable because of their prioritization of OHSS, but that ignored the article, makes this citation rate possibly the most significant finding of the present study. (It should be noted that a 1996 article by IVF co-inventor Robert G. Edwards, written with Rogerio Lobo and Phillippe Bouchard,²⁷ which argued in a similar vein, elicited more than 70 citations, which suggests that an investigation of those responses, similar to the present pilot study, would be of value. In this regard, it is important to note that Edwards and J.C. Emperaire observed with disappointment in

2004²⁸ that the clinical scene appeared not to have heeded the earlier calls.)

I found that the 23 published responses and citations can be divided into the following four categories.

- Those that explicitly endorsed or reiterated the ethical stance of Abramov, Elchalal, and Schenker ($n = 2$);
- Those that expressed implicit or partial support ($n = 4$);
- Those that explicitly contested their claims ($n = 2$); and
- Those that ignored their specific ethical claims and cited the article for some other reason ($n = 15$).

Two articles explicitly endorsed or reiterated the claims of Abramov, Elchalal, and Schenker. In these, tone is of some import, as the articles also contained something of the urgency expressed by the Israeli authors. Jan Roest made the most robust statement of support, asserting "It seems time for a change in approach,"²⁹ specifically advocating that fewer follicles be stimulated. Roest stated, "One can seriously wonder whether the criteria for the application of ART are used strictly enough."³⁰ Edwards (with Empeiraire) continued his campaign for more "friendly" drug regimes, arguing in this case that it is "Time to revolutionize the triggering of ovulation."³¹ This article cites Abramov, Elchalal, and Schenker, although not directly in the context of its argument.

Partial support was expressed by Michael A. Graf and Robert Fischer, who wrote, "We read with interest the article on severe ovarian hyperstimulation syndrome (OHSS) and fully agree with the authors that overuse of high dose gonadotrophin stimulation protocols . . . has led to a rise in moderate and severe OHSS."³² They nonetheless advocate the use of a clinical response, the value of which is questioned by Abramov, Elchalal, and Schenker. George B. Inge, Peter R. Brinsden, and Kay T. Elder gave implicit support, questioning the value of high-yield egg recruitment, while Mohamed Aboulghar and Ragaa Mansour endorsed the value of low-dose protocols, and Meike L. Uhler and colleagues urged "preventative strategies . . . to avoid . . . OHSS."³³

Two articles explicitly refuted the claims of Abramov, Elchalal, and Schenker at the level of interpretation of data and regarding the validity of the argument they raised.³⁴ (See below for further discussion.) The remaining articles ignored the ethical challenge posed by Abramov, Elchalal, and Schenker, expressing concern about the effects of OHSS on female patients but mostly arguing for active clinical responses to the present situation.³⁵ This type of article appears to be the most typical representative of the existing OHSS literature. To the extent that these citations did not embrace the argument for restraint, they might be seen as missing the authors' intended point.

LANGUAGE AND ARGUMENTATION

Examining the language and argumentation of scientific literature is not a particularly original undertaking, but it seems worthwhile when considering a contemporary clinical scenario in which healthy patients are endangered by the treatment choices of their doctors. Some of the usages and arguments identified here across these studies are "generic" to ART literature; others relate specifically to the responses to Abramov, Elchalal, and Schenker.

Abramov, Elchalal, and Schenker's subtitle for an article clearly written out of sympathy for the plight of female patients ("A price we have to pay?") may perhaps have been suggested by the journal's editors. Nonetheless, the use of the word "we" conveys a sense of a closed shop or a limited ethical horizon, and is not likely to be directed to the women whose health the article concerns, rather to other members of the medical and scientific professions likely to read the journal. In fact, there is no sense in which the "price" of OHSS is paid by the clinicians. As one of the supportive articles noted, OHSS is "caused by doctors and paid for by patients."³⁶

Controlled ovarian hyperstimulation (COH; sometimes referred to as COS, controlled ovarian stimulation) is the clinical term for the use of fertility drugs, but it seems to be a misnomer for the procedure. As the literature indicates, there is a large number of cases in which a decidedly uncontrolled response occurs. (One

article, not among those that cited Abramov, Elchalal, and Schenker, explicitly acknowledged this irony and placed the word "controlled" in inverted commas.³⁷) The word "syndrome" is a relatively neutral term, which could refer either to a collection of externally created symptoms or to endogenous symptoms, but several of the authors went further in using the language of disease and epidemiology to describe manifestations of OHSS. Annick Delvigne and Serge Rozenberg referred to the "Epidemiology and prevention of ovarian hyperstimulation" and to the "prevention of . . . disease."³⁸ Trifon Lainas and colleagues referred to "grade 4 disease,"³⁹ while Zouhair O. Amarin argued that radical surgical intervention was necessitated in extreme OHSS emergencies, given "that recovery was not just part of the natural disease process."⁴⁰ While it could be argued that these are simply technical ways of talking about any physiological occurrence as it develops and subsides in a person's body, and should not be seen as significant when understood in lay terms, the use of "disease" rather than the more neutral term "condition," for example, nonetheless may serve to reinforce the idea of OHSS as an external phenomenon, with an origin that is out of the hands of the clinician. Indeed, as a way of describing the effects of the drugs, OHSS "toxicity" or even "poisoning" might be as valid as the term "syndrome."

From another view, while the word "epidemic" was used rhetorically and with some sense of irony in the original article, this characterization was challenged by one of the two articles that actively opposed it. Robert G. Forman argued, "They describe an 'epidemic' of OHSS. An epidemic would be defined as a widespread occurrence, or spread, of a disease. Even if the authors' estimation of a tripling of the number of cases of OHSS over a 10 year period is correct, this could hardly be considered an 'epidemic.'"⁴¹ One team reported "a woman with severe male factor infertility."⁴² The use of IVF for male factor infertility (in this case constituting around 40 percent of the clinic's caseload) is a notable development in the indications for an invasive procedure on women, but the use here of the word "severe" referring to the husband's condition, while describing interventions in relation to the woman, is revealing. It shows how far infertility — a "cultural" illness — is perceived as shared by two people, even as its treatment has major physical dangers for only one.

Of the 23 articles, 13 failed to note that OHSS is caused by doctors.⁴³ Instead, it was referred to variously as: "an important complication of COH";⁴⁴ "one of complications of ovulation stimulation";⁴⁵ "a complication of supraphysiologic ovarian stimulation";⁴⁶ "the most serious complication of controlled ovarian stimulation";⁴⁷ and "one of the common complications in ovarian stimulation with gonadotrophin."⁴⁸ In relation to the responses of clients' bodies to their treatments, two articles used terminology that implicitly shifted accountability from the clinician to the client: Andre C.D. van Loenen and colleagues wrote about "poor responders"⁴⁹ and Delvigne and Rozenberg referred to "rebel cases" of OHSS.⁵⁰

Perhaps more importantly, the choice of words that were used in the articles to describe the frequency of OHSS indicates a point at which scientific interpretation and questions of language overlap. While the figures used in several of the articles varied quite widely on the global incidence of OHSS (0.2 to 1.0 percent;⁵¹ up to 10 percent;⁵² approximately 10 percent⁵³) and of severe OHSS (0.2 to 1.0 percent;⁵⁴ 0.2 to 2 percent;⁵⁵ 0.5 to 5 percent;⁵⁶ 0.6 to 14 percent⁵⁷), verbal characterizations of the frequency of OHSS and severe OHSS in some cases appeared to be identified according to an arbitrary or selective use of terms. For example, one referred to OHSS (of any type) as "common" (Osamu Tokuyama and colleagues, citing incorrectly the figure of 0.2 to 1.0 percent⁵⁸) and another referred to severe OHSS as "rare," while citing a rate of up to one in 20.⁵⁹

The two articles that actively opposed the ethical proposition put forth by Abramov, Elchalal, and Schenker appeared to seek, principally, to relativize the adverse effects of ovarian hyperstimulation. Forman stated: "To put the data into perspective, severe OHSS has to be considered as one of the complications of ovulation stimulation and, in particular, of IVF treatment. Other potential life-threatening complications occur with similar frequency."⁶⁰ The author then cited the high rates of ectopic pregnancy and multiple pregnancy associated with IVF. The argumentative force of this is blunted, I suggest, by the admission that IVF, a treatment identified as dangerous by Abramov, Elchalal, and Schenker, is only made to seem more so when its other major risk factors are described. Forman continued: "Very few medical interventions are risk-free

and severe OHSS will remain a complication of IVF cycles despite all attempts at prevention."⁶¹ This ignored the clinical difference between IVF and most other medical interventions, which aim, generally, to remedy a physical problem, rather than solve an emotional one through physical means. R.S. Mathur and Julian M. Jenkins similarly committed what might be called a category error when they suggested that the absence of deaths in Abramov, Elchalal, and Schenker's figures for OHSS could have been interpreted favorably in the light of statistics for maternal mortality that were not specifically related to fertility treatments.⁶² It ignored that maternal mortality is not — or, not by definition — caused by doctors.

Pursuing the view of the figures cited by Abramov, Elchalal, and Schenker as a positive, rather than a problem, Forman notes the lower number of severe cases of OHSS in their study compared to the global figures they cited, and claimed, "I would regard their data as being reassuring rather than a cause for concern."⁶³ This reassurance appears to be essentially the expression of a preference about how to interpret the same statistics about clients' suffering. For Mathur and Jenkins, this approach led to two conclusions: the first represented patients' consent as the benchmark by which medical ethics are judged. "Patients need to be counselled about the risk of developing OHSS and its consequences, but in the end must be free to make an informed decision regarding the most effective treatment for their problems."⁶⁴ One might be led to ask: under what circumstances would patient consent *not* be the baseline for argument in defense of a treatment? Abramov, Elchalal, and Schenker posed the question of the ethical burden on clinicians, not only on clients, and in this way suggested that informed consent should not be regarded as the overriding standard for deciding on the treatment to be undertaken. My argument is that informed consent, understood in this way, is highly problematic in that it puts a possibly unfair onus on the client as the person responsible, when the clinician is doing something that his or her colleagues have suggested is unethical. To imagine that the point-of-consent is the only ethical moment of substance in ART is to deny, among other things, the need for and the significance of clinicians' own prior deliberations. The second conclusion of Mathur and Jenkins was a simple assertion of interpretative preference. Emphasizing the non-physiological aspects of IVF and the question of funding, they stated: "Certainly the risk of OHSS must not be used as an argument to deny funds or restrict access to assisted conception programmes which have the potential to alleviate the misery of childlessness."⁶⁵

FURTHER OBSERVATIONS

Several of the articles described clinical scenarios and recent developments in the treatment of OHSS that raised very serious questions about the directions of ART and suggested that there is a real loss of perspective about the meaning of patient care in ART. The "pre-emptive" electrode cauterization or laser vaporization of healthy ovaries has been performed in numerous instances to permanently destroy follicles in clients' ovaries that contributed to the production of the hormonal response symptomatic of OHSS. Discussed by several of the articles,⁶⁶ this so-called "surgical pre-treatment"⁶⁷ was presented as being among the current choices that were available to reduce the incidence of OHSS. Indeed, one article bewilderingly used the opportunity provided by Abramov, Elchalal, and Schenker to promote electrocautery as a response of choice.⁶⁸ Surgically inflicting irreversible damage on women's bodies in the name of preventing the natural response to a dose of drugs surely poses an ethical problem, which points back to the original question posed by Abramov, Elchalal, and Schenker: "How far should we go?" Surely the answer has to be "Not that far."

In two emergency cases that led to similar irreversible results, a clinician removed (or caused to be removed) a substantial section of the ovaries of two women who suffered from severe OHSS.⁶⁹ The author, Amarin, admitted that the decision to remove a segment of the clients' ovaries (30 percent from each ovary in each woman) might have been interpreted as an aggressive treatment, but justified it on the basis of its lifesaving nature. In a narrow sense, this is, of course, true. But such horrendous scenarios seem to call for a greater degree of soul-searching for more responsible initial treatments, as proposed by Abramov, Elchalal, and Schenker. Another article, by Uhler and colleagues, described the near-fatal experience of a woman who was hospitalized for 47 days with critical OHSS and spent a further 30 days in rehabilitation clinics follow-

ing emergency treatment for a perforated duodenal ulcer.⁷⁰ The article was inconclusive about the relative causal weight that should have been attached to the OHSS itself, and to the subsequent risky surgical interventions used in response to it. The scenarios described in both articles made clear that, in all three cases, the women concerned came near to death, the ovaries of each swelled to the size of a softball, and approximately 2.5 to 5 liters of excess fluid were drained from their peritoneum. Each report mentioned the patients' stress (in the context of determining clinical scenarios): Amarin reported that a patient's "severe anxiety associated with invasive monitoring and multiple medical therapies in the intensive care unit" was a factor in the decision to proceed to laparotomy and bilateral partial oophorectomy,⁷¹ and Uhler and colleagues reported that the "profound stress associated with the combination of critical OHSS and subsequent required complex care as well as the diagnosis of *H. Pylori* [a bacterial condition that can cause stomach ulcers] were likely the causative factors of her perforated duodenal ulcer."⁷² (However, "stress" in the second example may have been intended to mean the purely physical effect of the treatments.)

The existence of the vast literature of OHSS heightens awareness of the largely experimental nature of much IVF treatment. One of the articles described a prospective trial of three different stimulation regimes that had been carried out on 38 IVF patients, which gave no indication that the patients were advised that they were part of a trial, nor that they gave consent for this, nor did the authors refer to ethical clearance on the part of their institution.⁷³ That article was nonetheless in the minority in admitting the experimental nature of the clinical choices. (One further article thanked its participants.⁷⁴) Most did not describe what the clinics were doing as experimental. While it could be argued that the analysis of clinical case notes in the interests of patients' welfare did not constitute experimentation, as such, the existence of a vast body of medical research literature, and the likelihood that such publishing is smiled upon at the institutions at which the authors were employed, together with the apparent competition between new approaches as they were carried out at the clinical level, makes a *de facto* "evidence-based" case for the largely experimental nature of much of this clinical culture. In effect, the literature of OHSS documents the explosion of a patient-funded research culture.

Moreover, it has been noted by a group of concerned practitioners that the fact that IVF is carried out largely in the private sector — "an environment not usually focused on well-conducted clinical trials" — along with the influence of the pharmaceutical industry and the relative lack of direct research funding, leads to "the early implementation of poorly validated strategies."⁷⁵ Two articles studied here refer to the possible under-reporting of cases of OHSS, which suggests something of the limits of self-regulation.⁷⁶ This situation also goes some way to explaining why research choices appear to have generally not included studies on the long-term effects of OHSS, including its psychological effects, nor indeed studies of the long-term effects of the drugs on those women who did not contract OHSS.⁷⁷ (Such a narrow focus is not unique to the ART industry: a 2004 article in *New Scientist* on the subject of the risks of IVF made no mention of the potential risk of ovarian hyperstimulation syndrome to mother or child.⁷⁸ Adhering to the traditional notion that the central issue in any discussion of reproductive technology is the sought-for child, the article lazily discusses only one survey of the health outcomes of children born through IVF and ICSI — intra-cytoplasmic sperm injection — rather than taking the five minutes required to do a PubMed or web search on a subject such as "*in vitro* fertilization risks.")

These research questions are, therefore, also fundamentally ethical questions. If there is no demonstrable will among clinicians to pursue these concerns, and if their priorities continue to be to promote the success rates of their own clinics, where will the impetus come from to answer questions about the long term? Divisions between clinicians and endocrinologists appear to exist,⁷⁹ and it seems that those practitioners who have been drawing attention to the risks of the drugs are the senior members of the profession, including Robert G. Edwards, René Frydman, and Joseph G. Schenker.⁸⁰ This "senatorial" initiative suggests both something of the anxiety created by ever-new drug regimes and the widening indications for IVF, and may be a crucial factor in bringing about change in a largely self-regulating industry.

DISCUSSION

The article by Abramov, Elchalal, and Schenker should be lauded as a valuable example of medical introspection. It is a modest but sincere attempt to flag to the community of ART researchers that there is an ethical question at stake, implicitly *even when* women are agreeing to undergo these procedures. If the question was: *What happens when, from the midst of a professional group, someone challenges some of the cherished assumptions of the group?* The answer might appear to be: *Not a great deal.* But it's important to note that, in this small exercise of ethical profiling, there are many signs of genuine debate and genuine critique. The critics in the profession are substantially in the minority, but they are present, when even 10 years ago, scarcely a sound was made, while the statistics presently available were mounting up in the clinical context.

I think it is possible to use this survey to provide a preliminary "snapshot" or cross-section of the research culture in which the clinical realities of OHSS arise. It is possible, at least, to suggest that such a seemingly low impact for an article that presents statistics about iatrogenic harm speaks either of a greater preoccupation with producing research literature than reading it, or of an alarming level of indifference, a "tin ear" to ethical pleas coming even from within the sector. The small number of articles that responded directly to Abramov, Elchalal, and Schenker, in the terms in which it posed its question, similarly speaks of a high level of selective reading. The impression that a lay reader gains is of a large medical culture that is extremely productive in terms of clinical intervention, yet apparently unwilling to confront the realities of the harm these interventions are causing. How can this situation come about? I have argued here that selective reading of the clinical literature, and secondarily, the ways in which language and argumentation are used, can help to maintain a degree of cultural insularity, something that can, in turn, contribute to what has been referred to elsewhere as "culturally induced moral ignorance."⁸¹

In many ways, the article by Abramov, Elchalal, and Schenker might be compared to that written by Henry K. Beecher in 1966,⁸² as an attempt both to challenge and, to some extent, to "blow the whistle" on colleagues. Several of Beecher's examples similarly came from clinical reports, rather than from prospective, designed research trials. While figures such as Beecher are rightly celebrated, it is easy to forget that exposés only become exposés after a long process of examination, and that the passage to reform is seldom instantaneous, and certainly cannot be assumed to be going to occur. For the purposes of bioethics teaching among trainee health professionals, this is an important lesson. When history is represented as a *fait accompli*, it is very difficult to escape from the conviction that what happened was always going to happen. Yet in the present instance, none of the researchers whose writing has been addressed here appears to have been tempted to go, for example, to the mainstream media, nor indeed to any governing body that may exist in their country to say, "we need regulation." Whistle-blowing does not always or automatically entail major institutional change.

Generally ART regulation and the ethical debate that accompanies it have been so dominated by debate about the status of the embryo — again, a political and politicized question — that the clinical realities and severe risks of ART tend to be ignored. The article by Abramov, Elchalal, and Schenker is a relatively rare example in which the risks of OHSS are aligned directly with the ethical questions that surround IVF. Such alignment was attempted in some government investigations⁸³ and was briefly mentioned in a policy-oriented monograph on egg donation.⁸⁴ Most feminist responses to ART have tended to overlook the basic clinical features of ART, preferring to address ethical questions about the apportioning of rights and the question of female giving.⁸⁵ The exception to this are the early contributions made by so-called radical feminists, who drew attention to problems with IVF drugs in the 1980s and early 1990s.⁸⁶ It is a great irony that the dominant theme in the reproductive technology culture — that all men and women, as "health consumers," have a right to access whatever means may be necessary to have a child to call biologically their own — should almost totally obliterate informed discussion about the physical/psychological health status of women whose reproductive rights are ostensibly so paramount.

A final reflection: if the problem of OHSS persists, that is, if the production of high egg yields is still

almost universally considered ethical, it may only be a matter of time before maturation of eggs *in vitro*, a possibility researched since the 1980s, but still relatively rare,⁸⁷ will be heralded as the solution to the problem. The seriousness of OHSS will finally be acknowledged, once the technological means to avoid it has been found. Should this occur, it must not be forgotten that ART clients — as many as 100,000 of whom will have suffered from excessive stimulation — are likely to have donated many of the eggs and much of the ovarian tissue used in the research to make this procedure feasible.⁸⁸

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NOTES

1. Y. Abramov, U. Elchalal, and J.G. Schenker, "Severe OHSS: An 'Epidemic' Of Severe OHSS: A Price We Have To Pay?" *Human Reproduction* 14, no. 9 (1999): 2181-3. The present article addresses mainly the question of eggs used for primary IVF treatment and for IVF using donor eggs. The donation of eggs for laboratory research, such as the production of embryonic stem cells, naturally raises questions relevant to the ethical issues discussed by Abramov, Elchalal, and Schenker, but would require a much lengthier discussion than is possible here.

2. R.G. Edwards, R. Lobo, and P. Bouchard, "Time to Revolutionize Ovarian Stimulation," *Human Reproduction* 11, no. 5 (1996): 917-9; R.G. Edwards, R. Lobo, and P. Bouchard, "Why Delay the Obvious Need for Milder Forms of Ovarian Stimulation?" *Human Reproduction* 12, no. 2 (1997): 399-401; J.C. Empeaire and R.G. Edwards, "Time to Revolutionize the Triggering of Ovulation," *Reproductive BioMedicine Online* 9, no. 5 (2004): 480-3; F. Olivennes and R. Frydman, "Friendly IVF: The Way of the Future?" *Human Reproduction* 13, no. 5 (1998): 1121-4; B.C. Fauser et al., "Minimal Ovarian Stimulation for IVF: Appraisal of Potential Benefits and Drawbacks," *Human Reproduction* 14, no. 11 (1999): 2681-6.

3. Royal Commission on New Reproductive Technologies (Canada), *Proceed With Care: Final Report of the Royal Commission on New Reproductive Technologies*, 2 vols. (Ottawa: Minister of Government Services, 1993), 1:391-424, 527-34; Task Force on Life and the Law, *Assisted Reproductive Technologies: Analysis and Recommendations for Public Policy* (New York: New York State Task Force on Life and the Law, 1998), 42-57.

4. See C.B. Cohen, ed., *New Ways of Making Babies: The Case of Egg Donation*, commissioned by the National Advisory Board on Ethics in Reproduction (Bloomington, Ind.: Indiana University Press, 1996), especially the chapter by Rosemary Tong, "Toward a Feminist Perspective on Gamete Donation and Reception Policies," pp. 138-155; K. Rothenberg, "Feminism, Law and Bioethics," *Kennedy Institute of Ethics Journal* 6, no. 1 (1996): 69-84.

5. M.A. Aboulghar and R.T. Mansour, "Ovarian Hyperstimulation Syndrome: Classifications and Critical Analysis of Preventive Measures," *Human Reproduction Update* 9, no. 3 (2003): 275-89, p. 275.

6. Empeaire and Edwards, "Time to Revolutionize the Triggering of Ovulation," see note 2 above.

7. See note 1 above, p. 2181.

8. Edwards, Lobo, and Bouchard, "Time to Revolutionize Ovarian Stimulation," see note 2 above, p. 917.

9. P.E. Egbase, "Severe OHSS: How Many Cases are Preventable?" *Human Reproduction* 15, no. 1 (2000): 8-10, p. 8.

10. See note 1 above; see note 9 above, p. 8.

11. Fauser et al., see note 2 above, p. 2681.

12. R.S. Mathur and J.M. Jenkins, "Is Ovarian Hyperstimulation Syndrome Associated with a Poor Obstetric Outcome?" *British Journal of Obstetrics and Gynaecology* 107, no. 8 (2000), 943-6, p. 943.

13. See note 5 above, p. 275.

14. See note 1 above, p. 2181; A. Delvigne and S. Rozenberg, "Epidemiology and Prevention of Ovarian Hyperstimulation Syndrome (OHSS): A Review," *Human Reproduction Update* 8, no. 6 (2002): 559-77, p. 559.

15. Task Force on Life and the Law, see note 3 above, pp. 47-9.

16. Delvigne and Rozenberg, see note 14 above, p. 559.

17. G.B. Inge, P.R. Brinsden, and K.T. Elder, "Oocyte Number Per Live Birth in IVF: Were Steptoe and Edwards Less Wasteful?" *Human Reproduction* 20, no. 3 (2005): 588-92.

18. Edwards, Lobo, and Bouchard, "Time to Revolutionize Ovarian Stimulation," see note 2 above, p. 917; see note 1 above, p. 2182.

19. See note 5 above, p. 285.

20. See note 1 above, p. 2181.

21. Ibid.

22. Ibid., 2182.

23. Ibid.

24. Ibid.

25. T. Lainas et al., "Administration of Methylprednisolone to Prevent Severe Ovarian Hyperstimulation Syndrome in Patients Undergoing In Vitro Fertilization," *Fertility and Sterility* 78, no. 3 (2002): 529-33.

26. R.S. Mathur and J.M. Jenkins, "Patients Should be Allowed to Weigh the Morbidity of OHSS Against the Benefits of Parenthood," *Human Reproduction* 14, no. 9 (1999): 2183-5. I thank Heather Wolfram for detecting this discrepancy.

27. Edwards, Lobo, and Bouchard, "Time to Revolutionize Ovarian Stimulation," see note 2 above.

28. Empeaire and Edwards, "Time to Revolutionize the Triggering Ovulation," see note 2 above.

29. J. Roest, "Severe OHSS: An 'Epidemic' Caused by Doctors," *Human Reproduction* 14, no. 9 (1999): 2183.

30. Ibid.

31. Empeaire and Edwards, "Time to Revolutionize the Triggering of Ovulation," see note 2 above.

32. M.A. Graf and R. Fischer, "Severe OHSS: An 'Epidemic' of Severe OHSS: A Price We Have to Pay?" *Human Reproduction* 14, no. 12 (1999), p. 2930.

33. See note 17 above; see note 5 above, p. 285; M.L. Uhler et al., "Perforated Duodenal Ulcer Associated with Ovarian Hyperstimulation Syndrome," *Human Reproduction* 16, no. 1 (2001): 174-6, p. 175.

34. See note 26 above; R.G. Forman, "Severe OHSS: An Acceptable Price?" *Human Reproduction* 14, no. 11 (1999): 2687-8.

35. See note 9 above; see note 12 above; A. Delvigne and S. Rozenberg, "Preventive Attitude of Physicians to Avoid OHSS in IVF Patients," *Human Reproduction* 16, no. 12 (2001): 2491-5; M. Filicori and G.E. Cognigni, "Roles and Novel Regimens of Luteinizing Hormone and Follicle-stimulating Hormone in Ovulation Induction," *Journal of Clinical Endocrinology and Metabolism* 86, no. 4 (2001): 1437-41; L. Shanner and J. Nisker, "Bioethics for Clinicians: 26. Assisted Reproductive Technologies," *Canadian Medical Association Journal* 164, no. 11 (2001): 1589-94; O. Tokuyama et al., "Vascular Endothelial Growth Factor Concentrations in Follicular Fluid Obtained from IVF-ET Patients: A Comparison of hMG, Clomiphene Citrate, and Natural Cycle," *Journal of Assisted Reproductive Genetics* 19, no. 1 (2002): 19-23; see note 25

above; Delvigne and Rozenberg, see note 14 above; A. Raziel et al., "Increased Early Pregnancy Loss in IVF Patients with Severe Ovarian Hyperstimulation Syndrome," *Human Reproduction* 17, no. 1 (2002): 107-10; A.C.D. van Loenen et al., "GnRH Agonists, Antagonists, and Assisted Conception," *Seminars in Reproductive Medicine* 20, no. 4 (2002): 349-64; P.Y. Liu and D.J. Handelsman, "The Present and Future State of Hormonal Treatment for Male Infertility," *Human Reproduction Update* 9, no. 1 (2003): 9-23; Z.O. Amarin, "Bilateral Partial Oophorectomy in the Management of Severe Ovarian Hyperstimulation Syndrome — an Aggressive, but Perhaps Life-saving Procedure," *Human Reproduction* 18, no. 4 (2003): 659-64; E. Aktan et al., "Effects of Coasting on the Outcome of Intracytoplasmic Sperm Injection-Embryo Transfer Cycles," *Australian and New Zealand Journal of Obstetrics and Gynaecology* 44, no. 4 (2004): 298-301; R. Klemetti et al., "Complications of IVF and Ovulation Induction," *Human Reproduction* 20, no. 12 (2005): 3293-300; E. Thyzel et al., "Age Dependent Assessment of TFPI Levels in Follicular Fluid of Women Undergoing IVF," *Clinica Chimica Acta* 361, no. 1-2 (2005): 176-81.

36. See note 29 above, p. 2183.

37. Fauser et al., see note 2 above, p. 2682.

38. Delvigne and Rozenberg, see note 14 above, p. 572.

39. See note 25 above, p. 531.

40. Amarin, see note 35 above, p. 662.

41. Forman, see note 34 above, p. 2687.

42. Raziel et al., see note 35 above, p. 109.

43. See note 12 above; see note 17 above; see note 25 above; Forman, see note 34 above; see note 32 above; Filicori and Cognigni, see note 35 above; Liu and Handelsman, see note 35 above; Shanner and Nisker, see note 35 above; Tokuyama et al., see note 35 above; Uhler et al., see note 33 above; van Loenen et al., see note 35 above; Klemetti et al., see note 35 above; Aktan et al., see note 35 above.

44. Van Loenen et al., see note 35 above, p. 356.

45. Forman, see note 34 above, p. 2687.

46. See note 12 above, p. 943.

47. Uhler et al., see note 33 above, p. 174.

48. Tokuyama et al., see note 35 above, p. 19.

49. Van Loenen et al., see note 35 above, p. 354.

50. Delvigne and Rozenberg, see note 14 above, p. 572.

51. Tokuyama et al., see note 35 above, p. 21.

52. See note 9 above, p. 8.

53. Amarin, see note 35 above, p. 659.

54. See note 1 above, p. 2181.

55. Amarin, see note 35 above. This figure appears to be cited for IVF only.

56. Delvigne and Rozenberg, see note 14 above, p. 559.

57. See note 25 above, p. 529.

58. Tokuyama et al., see note 35 above, p. 19. Their citation refers to Abramov, Elchalal, and Schenker (see note 1 above, p. 2181), which gives this figure for severe OHSS only, not for all forms.

59. Delvigne and Rozenberg, see note 14 above, p. 559.

60. Forman, see note 34 above, p. 2687.

61. *Ibid.*, 2688.

62. See note 26 above, p. 2185.

63. Forman, see note 34 above, p. 2687.

64. See note 26 above, p. 2185.

65. *Ibid.*

66. See note 5 above; see note 9 above; Delvigne and Rozenberg, see note 14 above; Amarin, see note 35 above, p. 662.

67. Delvigne and Rozenberg, see note 14 above, p. 572.

68. See note 9 above, p. 9.
69. Amarin, see note 35 above.
70. Uhler et al., see note 33 above.
71. Amarin, see note 35 above, p. 661.
72. Uhler et al., see note 33 above, p. 175.
73. Tokuyama et al., see note 35 above, pp. 19-23.
74. See note 25 above, p. 533.
75. Fauser et al., see note 2 above, p. 2685.
76. Forman, see note 34 above, p. 2687; Raziel et al., see note 35 above, p. 109 (citing Forman).
77. See note 26 above, p. 2184.
78. J. Randerson, "IVF Seems Safe But Only Time Will Tell," *New Scientist* 184, no. 2471 (30 October - 5 November 2004): 10-11.
79. Edwards, Lobo, and Bouchard, "Why Delay the Obvious Need?" see note 2 above.
80. Edwards, Lobo, and Bouchard, "Time to Revolutionize Ovarian Stimulation," see note 2 above; Edwards, Lobo, and Bouchard, "Why Delay the Obvious Need?" see note 2 above; Empeaire and Edwards, "Time to Revolutionize the Triggering of Ovulation," see note 2 above; Olivennes and Frydman, see note 2 above; see note 1 above.
81. U.S. Department of Energy, *Advisory Committee on Human Radiation Experiments: Roadmap to the Project*, chap. 4, http://www.eh.doe.gov/ohre/roadmap/achre/chap4_2.html, accessed 12 July 2005.
82. H.K. Beecher, "Ethics and clinical research," in *Bioethics: An Anthology*, ed. H. Kuhse and P. Singer (Malden, Mass.: Blackwell Publishing, 1999), 421-8.
83. See note 3 above.
84. Cohen, see note 4 above, pp. 272-3; cf. A.D. Gurmankin, "Risk Information Provided to Prospective Oocyte Donors in a Preliminary Phone Call," *American Journal of Bioethics* 1, no. 4 (2001): 3-13.
85. Rothenberg, see note 4 above; Tong, see note 4 above.
86. R. Klein, *The Exploitation of a Desire* (Geelong: Women's Studies Summer Institute, distributed by Deakin University Press, 1989); R. Rowland, *Living Laboratories: Women and Reproductive Technologies* (Bloomington, Ind.: Indiana University Press, 1992).
87. See note 32 above; P. Curtis, "Better than sex — IVF clinic claims to beat nature at its own game," *Guardian*, 30 December 2006, <http://www.guardian.co.uk/print/0,,329673062-110418,00.html>, accessed 23 March 2007.
88. Indeed, in December 2006, subsequent to this article's acceptance the previous June, a new society was formed, the International Society of Minimally Assisted Reproduction, with this specific aim in mind. See <http://www.naturalcycle.org>, accessed 23 March 2007.