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## Marking the Fine Line: Ethics and the Regulation of Innovative Technologies in Human Reproduction

Anne Drapkin Lyerly\*

I don't remember Mr. Steptoe saying his method of producing babies had ever worked, and I certainly didn't ask. I just imagined that hundreds of children had already been born through being conceived outside their mothers' wombs.

Lesley and John Brown<sup>1</sup>

### I. INTRODUCTION

On July 25, 1978 in England, Louise Brown became the first baby born by in vitro fertilization (IVF).<sup>2</sup> Three years later, Elizabeth Carr followed suit as the first "test tube baby" born in the United States.<sup>3</sup> Since then, much has changed in the field of human reproduction. Once reported "with a fervor not seen since the first moon landing,"<sup>4</sup> the birth of a child from IVF now accounts for more than one in sixty births in the UK,<sup>5</sup>

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1. LESLEY BROWN & JOHN BROWN WITH SUE FREEMAN, *OUR MIRACLE CALLED LOUISE: A PARENT'S STORY* 106 (Paddington Press 1979).

2. LORI B. ANDREWS, *THE CLONE AGE: ADVENTURES IN THE NEW WORLD OF REPRODUCTIVE TECHNOLOGY* 15 (1999).

3. *Id.* at 31.

4. *Id.* at 15.

5. Human Fertilisation & Embryology Authority, Latest UK IVF Figures—2007 (Sept. 30, 2009), <http://www.hfea.gov.uk/ivf-figures-2006.html#1279> (last visited Apr. 22, 2010) (noting that "[a]round 1.5% of all births and 1.8% of all babies born in the UK are the result of IVF and donor

approximately one in eighty babies in the United States,<sup>6</sup> and assisted reproductive technologies (ARTs) constitute a burgeoning medical practice worldwide. More than three million children have been created by IVF;<sup>7</sup> the United States alone can boast of more than 41,300 births per year resulting in 54,600 babies per year (due to twins, triplets, and higher order multiple gestations)<sup>8</sup> and generating an annual revenue of nearly 3 billion dollars.<sup>9</sup>

Indications for ARTs and the level of technological and scientific sophistication have expanded as well. Originally developed as a means to overcome infertility resulting from damaged fallopian tubes, ARTs are now used to address other sources of infertility, such as ovulation problems and endometriosis in women, poor sperm quality or function in men, and unexplained causes of failed conception.<sup>10</sup> The ability to fertilize and manipulate embryos outside the womb has also led to the development of techniques to screen for genetic disease and selectively implant only “healthy” embryos. In the midst of the rapid evolution of ARTs, however, one aspect of the field has remained remarkably constant in the United States: there has been virtually no effective regulatory protection for the human subjects who participate in or who are affected by the process of innovating new techniques in reproductive medicine.

With the highly publicized scandals associated with the fertility industry, calls for more regulation of ARTs in the

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insemination”).

6. See CTRS. FOR DISEASE CONTROL & PREVENTION, DEP’T OF HEALTH & HUMAN SERVS., NATIONAL VITAL STATISTICS REPORTS, Jan. 7, 2009, at 1, available at [http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\\_07.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_07.pdf) [hereinafter FINAL DATA FOR 2006] (stating that “[a] total of 4,265,555 births were registered in the United States in 2006); CTRS. FOR DISEASE CONTROL & PREVENTION ET AL., DEP’T OF HEALTH & HUMAN SERVS., 2006 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES 61 (2008), available at <http://www.cdc.gov/art/ART2006/508PDF/2006ART.pdf> [hereinafter 2006 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES] (stating that in 2006 54,656 infants were born that were conceived using ART procedures).

7. Zev Rosenwaks & Kristin Bendikson, Commentary, *Further Evidence of the Safety of Assisted Reproductive Technologies*, 104 PROC. NAT’L ACAD. SCI. 5709, 5709 (2007), available at <http://www.pnas.org/content/104/14/5709.full.pdf+html>.

8. 2006 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES, *supra* note 6, at 61.

9. DEBORA L. SPAR, *THE BABY BUSINESS: HOW MONEY, SCIENCE, AND POLITICS DRIVE THE COMMERCE OF CONCEPTION* 32–33 (2006).

10. *Id.* at 1–2.

United States have been frequent and emphatic. Indeed, the birth of octuplets last year inspired vigorous debate about the adequacy and role of professional guidelines as arbiters of appropriate and safe care.<sup>11</sup> Yet, the best of the dialogue—especially of late—has focused primarily on regulation of *practice*.

For example, such debates focus on how we ought to regulate the exchange of gametes;<sup>12</sup> whether there should be stricter limits on how many embryos can be transferred to a woman's uterus during a single cycle; whether the informed consent process should be standardized; whether insurance coverage for fertility treatment ought to be mandated;<sup>13</sup> whether access to ARTs can be ethically restricted based on age, health, sexual orientation. These are all important questions, indeed. But far less attention has been directed at the regulation of *research*—of oversight for the process of moving from bench to bedside, innovation to practice. If we are concerned about the safe and ethical provision of reproductive medicine in the 21st century, the role of regulation of this process is a topic that deserves, at the very least, our equal attention.

This paper aims to pry apart and highlight the particular issue of innovation in reproductive medicine as distinct from other areas of controversy in regulating this field, and one for which the case for regulation is particularly strong. It begins with a description of a clinical case that exemplifies the nature of and problems associated with the lack of regulatory oversight. Next, follows a description of factors that have contributed to the current state of affairs. The paper then articulates three reasons why better oversight for innovation is ethically necessary, and concludes with four opportunities for potential progress.

## II. UNREGULATED INNOVATION: A CLINICAL EXAMPLE

Perhaps well known by now is a clinical case that

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11. See, e.g., Howard Minkoff & Jeffrey Ecker, *The California Octuplets and the Duties of Reproductive Endocrinologists*, 201 AM. J. OBSTETRICS & GYNECOLOGY 15.e1, 15.e1 (2009); John A. Robertson, *The Octuplet Case—Why More Regulation is Not Likely*, 39 HASTINGS CENTER REP., May 2009, at 26, 27.

12. See NAOMI R. CAHN, TEST TUBE FAMILIES: WHY THE FERTILITY MARKET NEEDS LEGAL REGULATION 146 (2009).

13. See Naomi R. Cahn & Jennifer M. Collins, *Eight is Enough*, 103 NW. U. L. REV. 501, 503–04 (2009), available at <http://www.law.northwestern.edu/lawreview/colloquy/2009/22/LRColl2009n22Cahn&Collins.pdf>.

exemplifies the lack of regulation of innovation in reproductive medicine and reasons for concern. In 1992, a new technique to achieve fertilization known as ICSI (intracytoplasmic sperm injection) was introduced in Belgium as a treatment for male factor infertility.<sup>14</sup> The technique involves the injection of a single sperm into an egg to achieve fertilization (as opposed to standard IVF, in which sperm and eggs are mixed together, allowing fertilization to occur spontaneously).<sup>15</sup> Within a year of the first reported ICSI pregnancy in Belgium, the technique was introduced in the United States and quickly became widely utilized by many programs.<sup>16</sup> By 1997, an average of 30% of U.S. ART cycles used ICSI,<sup>17</sup> with some centers using the technique in as many as 73% of all cycles.<sup>18</sup> By 2006, the percent of fresh cycles using ICSI cycles had climbed to 62% overall.<sup>19</sup> Equally striking is the fact that this dramatic rise in ICSI curiously occurred while the proportion of patients receiving treatment for male-factor infertility remained stable.<sup>20</sup>

Amidst the enthusiasm regarding this innovative technology, concerns about safety surfaced. No experimental phase preceded its introduction, in part due to absence of an adequate experimental model,<sup>21</sup> and in part due to “its immediate and overwhelming success.”<sup>22</sup> But as children conceived by ICSI were evaluated in Europe, data regarding short and long-term outcomes suggested that some may be at

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14. Gianpiero Palermo et al., *Pregnancies After Intracytoplasmic Injection of Single Spermatozoon into an Oocyte*, 340 LANCET 17, 17–18 (1992).

15. Gina Kolata, *New Pregnancy Hope: A Single Sperm*, N.Y. TIMES, Aug. 11, 1993, at C11.

16. *Id.*

17. CTRS. FOR DISEASE CONTROL & PREVENTION ET AL., DEP'T OF HEALTH & HUMAN SERVS., 1997 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES 25 (1999), available at <http://www.cdc.gov/art/ArchivedARTPDFs/97art.pdf> [hereinafter 1997 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES].

18. *Id.* at 127 (citing the Fertility Institute of Northwest Florida).

19. 2006 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES, *supra* note 6, at 39.

20. See Tarun Jain & Ruchi S. Gupta, *Trends in the Use of Intracytoplasmic Sperm Injection in the United States*, 357 NEW ENG. J. MED. 251, 251 (2007).

21. See R. Yanagimachi, *Is an Animal Model Needed for Intracytoplasmic Sperm Injection (ICSI) and Other Assisted Reproduction Technologies?*, 10 HUM. REPROD. 2525, 2526 (1995).

22. E. R. te Velde et al., Commentary, *Concerns About Assisted Reproduction*, 351 LANCET 1524, 1524 (1998).

increased risk for health problems. Some studies suggested an increased risk of abnormalities in sex<sup>23</sup> and autosomal chromosomes.<sup>24</sup> Follow-up of developmental parameters in children conceived by ICSI also suggested that there may be an increased risk of mild developmental delay.<sup>25</sup> Other studies demonstrated a scientific basis for the possibility of an increased risk of neurodegenerative disease<sup>26</sup> and malignancy later in life<sup>27</sup> in children conceived by ICSI, and long-term consequences of the procedure remain unknown. In the absence of regulation regarding the introduction of this new ART, tens of thousands of children have been created by a technology of unproven safety.

Even if short and long term data eventually allay some of the safety concerns about ICSI (as some recently have, including a report demonstrating the absence of alterations in DNA point mutations in IVF embryos<sup>28</sup>), scores of concerns about the safety of fertility treatment in general remain. Such concerns are derived, at least in part, from the paucity of oversight that has governed the translation of ARTs into practice. Most recently, concerns have been broadly publicized about the impact of IVF on a process called “imprinting,” which involves changes in the pattern of gene expression. The concerns grew out of reports of an apparent increased frequency in rare genetic disorders in children conceived through both IVF and ICSI,<sup>29</sup> possibly attributable to the type of medium in which *in vitro* embryos are grown before they are placed in a woman’s body. Other data indicate an increased risk of heart defects, cleft lip, esophageal and anorectal atresia in infants conceived with ART, though the mechanisms behind

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23. See Peter In’t Veld et al., *Sex Chromosomal Abnormalities and Intracytoplasmic Sperm Injection*, 346 LANCET 773, 773 (1995).

24. See André Van Steirteghem et al., *Is ICSI the Ultimate ART Procedure?*, in INTERNATIONAL CONGRESS SERIES 1183, FERTILITY AND REPRODUCTIVE MEDICINE, 27, 33 (Roger D. Kempers et al. eds., 1998).

25. See Jennifer R. Bowen et al., *Medical and Developmental Outcome at 1 Year for Children Conceived by Intracytoplasmic Sperm Injection*, 351 LANCET 1529, 1532 (1998).

26. See Aneta T. Dowsing et al., *Linkage Between Male Infertility and Trinucleotide Repeat Expansion in the Androgen-Receptor Gene*, 354 LANCET 640, 640 (1999).

27. David Nudell et al., *Increased Frequency of Mutations in DNA from Infertile Men with Meiotic Arrest*, 15 HUM. REPROD. 1289, 1293 (2000) (noting a possible increase in risk of “somatic defects later in life”).

28. Rosenwaks & Bendikson, *supra* note 7, at 5709.

29. See Somjate Manipalviratn et al., *Imprinting Disorders and Assisted Reproductive Technology*, 91 FERTILITY & STERILITY 305, 313–314 (2009).

such trends remain uncertain.<sup>30</sup> Amidst efforts to reassure patients and the public, a growing consensus points to risks for offspring, and responsibility to identify and minimize them.<sup>31</sup>

Less attention has been directed at the equally concerning paucity of data on the implications of ARTs for the health and well-being of *women* whose bodies (and lives) interface with novel techniques. A 2008 Cochrane review of outcomes of interventions used in the treatment of infertility indicated that most randomized studies conducted since 2000 either did not measure the short or long term health impact of fertility treatment on women, or did not have sufficient power to detect meaningful differences in delivery rates or obstetric outcomes, particularly less frequent outcomes such as complications affecting maternal health.<sup>32</sup> Data regarding ARTs and breast and ovarian cancer are reassuring, but insufficient to rule out increased risk with treatment. Data on other health parameters indicate reason for worry. In particular, a higher likelihood of abnormal placentation disorders in women pregnant from IVF (pre-eclampsia, placenta previa, and placental abruption)<sup>33</sup> is not only immediately threatening to maternal health, but may be a harbinger of cardiovascular risk in mothers in the longer term. Despite the widespread use of ARTs, research on the long term impact of women's health treatment is scarce.

### III. REASONS FOR THE LACK OF OVERSIGHT

As the above suggests, innovation in human reproduction in the United States has not advanced under the regulatory oversight applied to other areas of research on human subjects. At least two forces at play help to explain why. First, an array of cultural, scientific, political and economic forces has served to dissociate reproductive medicine—innovative or otherwise—

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30. J. Reefhuis et al., *Assisted Reproductive Technology and Major Structural Birth Defects in the United States*, 24 HUM. REPROD. 360, 360 (2009).

31. See Gina Kolata, *Picture Emerging on Genetic Risks of IVF*, N.Y. TIMES, Feb. 17, 2009, at D1 [hereinafter *Picture Emerging on Genetic Risks of IVF*].

32. AGENCY FOR HEALTHCARE RESEARCH & QUALITY, DEP'T OF HEALTH & HUMAN SERVS., EFFECTIVENESS OF ASSISTED REPRODUCTIVE TECHNOLOGY v (2008), *available at* <http://www.ahrq.gov/downloads/pub/evidence/pdf/infertility/infertility.pdf> [hereinafter EFFECTIVENESS OF ASSISTED REPRODUCTIVE TECHNOLOGY].

33. *Id.* at 111.

from its connotations as a research endeavor. Second, even for innovations that all would agree fall within the definition of research, traditional sources of regulatory control have not been applied.

#### A. RESEARCH AND PRACTICE

Reproductive medicine has come to occupy a unique locus on the spectrum of research and practice, largely as a result of the cultural, scientific, political, and economic contexts in which it has evolved. As Robert Blank observed more than a decade ago, the application of new technology has been generally dissociated from the term “experimentation,” raising concern “about whether participants are patients, subjects, or both.”<sup>34</sup> As a result, constraints which usually apply to other fields of medicine are not applied to reproductive medicine, and innovation in the field proceeds without protection of individuals who engage (as patients or participants) in novel reproductive interventions. Some of the forces that have worked to dissociate “innovation” from “research” or “experimentation” are discussed below.

##### 1. Cultural Backdrop

First, innovation in reproductive medicine has taken place against a cultural backdrop of *protectionist policies* toward women of childbearing potential, pregnant women, and fetuses. As described in the IOM report on Women and Health Research, two events in the 1960s and early 1970s “amplif[ie]d public sentiment about the need for greater protection for fetuses from risks in science and medicine.”<sup>35</sup> The discovery that thalidomide, a drug approved in twenty countries outside the United States for nausea in early pregnancy caused severe limb deformities in children powerfully fostered aversion to involving pregnant women and women of childbearing age in drug research.<sup>36</sup> The other event, the discovery that diethylstilbestrol (DES) caused a number of abnormalities of the genital tract in daughters of women who took the drug to prevent miscarriage, served to strengthen public sentiment

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34. Robert H. Blank, *Assisted Reproduction and Reproductive Rights: The Case of In Vitro Fertilization*, 16 POL. & LIFE SCI. 279, 283 (1997).

35. 1 COMM. ON THE ETHICAL AND LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN, INST. OF MED., WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 40 (Anna C. Mastroianni et al. eds., 1994).

36. *Id.*



opposing pharmaceutical innovation in women who were pregnant or of childbearing potential.<sup>37</sup> The FDA issued guidelines in 1977 that recommended exclusion of women of childbearing potential from early phases of drug trials.<sup>38</sup>

Although these events occurred in the setting of trials of drugs rather than the introduction of devices or procedures, the results of the exclusionary policy tell an important story about the consequences of “protection” from experimentation in general. Consider their impact on the knowledge base about post-conception reproductive medicine. The idea that women and fetuses can and should be protected *from* research, rather than *through* research has resulted in a profound dearth of information about the safety and appropriate use of medications during pregnancy.<sup>39</sup> Approximately two thirds of women are prescribed at least one medication other than a vitamin or mineral supplement during pregnancy.<sup>40</sup> Yet the evidence base for determining how and whether to dose such medications or treat illness during pregnancy is distressingly poor. Only a dozen medications are approved for use by the FDA during pregnancy and all are for gestation or birth related issues such as anesthesia or nausea.<sup>41</sup> Any medicine used to treat illness during pregnancy is prescribed without adequate data on dosing or safety. Paradoxically, protectionist policies have thrust innovation in drug therapy for pregnant women out of the protective umbrella of pharmaceutical regulation into the predominantly unregulated realm of off-label use.<sup>42</sup>

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37. *Id.* at 41.

38. See FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH, EDUC., & WELFARE, GENERAL CONSIDERATION FOR THE CLINICAL EVALUATION OF DRUGS 15–16 (1977).

39. See Anne Drapkin Lyerly et al., *Pregnancy and Clinical Research*, HASTINGS CENTER REP., Nov. – Dec. 2008, at 53, 53 [hereinafter *Pregnancy and Clinical Research*] (stating that “[I]f we are to treat pregnant women’s illnesses effectively—something crucial to the health of *both* pregnant women and the children they bear—we must study medications *in* pregnant women.”) (emphasis in original).

40. See Susan E. Andrade et al., *Prescription Drug Use in Pregnancy*, 191 AM. J. OBSTETRICS & GYNECOLOGY 398, 400 (2004) (finding that for 64% of deliveries in the study, “a drug other than a vitamin or mineral supplement was dispensed in the 270 days before delivery”).

41. Doris Haire, Nat'l Women's Health Alliance, *FDA Approved Obstetrics Drugs: Their Effects on Mother and Baby*, <http://www.nwhalliance.org/FDAAPPROVED.htm> (last visited Apr. 22, 2010) (providing a list and description of drugs approved for use by the FDA during pregnancy).

42. See Anne Drapkin Lyerly et al., *The Second Wave: Toward*

A related set of cultural factors has led to a dearth of research pertaining to the health of *women* who participate in ARTs: tendencies to overlook the gestating (or in the case of ARTs, potentially gestating) woman as a patient, subject, or research participant in her own right. Many have pointed out a longstanding and pervasive tendency in reproductive health to focus primarily or exclusively on risks and benefits to offspring to the exclusion of risks and benefits to women themselves.<sup>43</sup> The tendency can be attributed in part to approaches that regard the pregnant woman and her fetus as separate, which obscure “the physical and social relationship between pregnant woman and fetus, the ways that maternal and fetal physiologies and welfare are linked, and perhaps . . . the woman herself.”<sup>44</sup> Indeed, even in cases where innovative procedures in post-conception reproductive medicine have been recognized as research endeavors, maternal outcomes are often not measured. For instance, surgical interventions to correct birth defects *in-utero* have generated a notable paucity of studies measuring short and long-term outcomes for women, compared to those measuring the impact on children.<sup>45</sup> Recent efforts to redress the dearth of evidence have identified significant risks for women of pre-birth intervention.<sup>46</sup> And while the best known examples regard post-conception research (maternal-fetal surgery or research on AIDS during pregnancy) as opposed to ARTs, the tendency to overlook maternal health as an end in its own right spans the reproductive medicine from pre-conception to years after birth.<sup>47</sup>

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*Responsible Inclusion of Pregnant Women in Research*, INT’L J. FEMINIST APPROACHES TO BIOETHICS, Fall 2008, at 5, 7 [hereinafter *The Second Wave*].

43. See Ruth Faden et al., *Women as Vessels and Vectors: Lessons From the HIV Epidemic*, in FEMINISM AND BIOETHICS: BEYOND REPRODUCTION 252, 253 (Susan M. Wolf ed., 1996).

44. Anne Drapkin Lyerly et al., *A Critique of the ‘Fetus as Patient’*, AM. J. BIOETHICS, July 2008, at 42, 43 [hereinafter *A Critique of the ‘Fetus as Patient’*].

45. See Anne Drapkin Lyerly et al., *Toward the Ethical Evaluation and Use of Maternal-Fetal Surgery*, 98 AM. J. OBSTETRICS & GYNECOLOGY 689, 695–696 (2001) [hereinafter *Toward the Ethical Evaluation and Use*].

46. Kristin Golombeck et al., *Maternal Morbidity After Maternal-Fetal Surgery*, 194 AM. J. OBSTETRICS & GYNECOLOGY 834, 838 (2006) (finding that “short-term maternal morbidity is related directly to the invasiveness of the technique”).

47. Anne Drapkin Lyerly et al., *Commentary, The National Children’s Study: A Golden Opportunity to Advance the Health of Pregnant Women*, 99 AM. J. PUB. HEALTH 1742, 1742 (2009) [hereinafter *The National Children’s Study*].

## 2. Scientific & Cultural Context

A second force separating ARTs from connotations of research and outside its regulatory protections is their scientific and clinical context. A significant proportion of innovation in reproductive medicine involves medical *procedures*, which lack the explicit regulatory mechanisms for ensuring safety and efficacy that apply to drugs.<sup>48</sup> Reproductive medicine shares with other procedure-related specialties, such as general surgery, an exemption from the strenuous research and approval process applied to pharmaceuticals. In his testimony to the National Bioethics Advisory Commission (NBAC) on July 11, 2000, Dr. Sam Wells, Director of Clinical Trials and Evidence Based Medicine for the American College of Surgeons noted how surgery has “fallen under the radar screen of oversight and surveillance,” since there is “no FDA for surgery. . . .”<sup>49</sup> As a result, new procedures may be performed and integrated into clinical practice without proof of safety, efficacy, or superiority to standard therapy.<sup>50</sup>

Furthering the challenges engendered by its status as a surgical specialty, the endpoints assessed in innovative procedures in reproductive medicine make assumptions about their therapeutic status arguably more likely. For the end result of ARTs is measured not in a clinical parameter such as blood pressure or cholesterol, cancer-free survival, even quality of life, but in the presence or absence of a child. Indeed, as Andrea Bonnicksen recently observed, “it appears that ARTs are efficacious in that the key outcome, the take-home baby rate, has steadily improved for most programs.”<sup>51</sup> Indeed, it may unpalatable for many to think of child as the successful

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48. See generally Charles B. Wilson, *Adoption of New Surgical Technology*, 332 BRIT. MED. J. 112 (2006) (arguing that new surgical technologies should be subjected to a higher level of scrutiny); see also Steven M. Strasberg & Philip A. Ludbrook, *Who Oversees Innovative Practice? Is There a Structure that Meets the Monitoring Needs of New Techniques?*, 196 J. AM. C. SURGEONS 938, 946 (2003) (arguing that agency oversight is needed for new surgical techniques).

49. Samuel A. Wells, Jr., Dir. of Clinical Trials & Evidence-Based Medic., Am. Coll. of Surgeons, Statement at a Meeting of the National Bioethics Advisory Commission (Jan. 11, 2000), at 226, available at <http://bioethics.georgetown.edu/nbac/transcripts/july00/7-00day2pt2.pdf>.

50. *Id.*

51. Andrea L. Bonnicksen, *Oversight of Assisted Reproductive Technologies: The Last Twenty Years*, in REPROGENETICS: LAW, POLICY, AND ETHICAL ISSUES 64, 81 (Lori P. Knowles & Gregory E. Kaebnick eds., 2007).

product of an experiment. Thus the clinical context in which innovation in reproductive medicine takes place further implements exceptionalism with respect to regulations and protections for individuals exposed to untested interventions.

### 3. Politics

Third, the political context in which new therapies in reproductive medicine are implemented has encouraged the dissociation of reproductive medicine from connotations of research. In the United States, a so-called “failure of political nerve,” has powerfully shaped the recalcitrance about regulation.<sup>52</sup> In the sphere of innovation, this recalcitrance is manifested most forcibly by the consistent failure, in the last four decades, by the federal government to provide funding for research on human embryos and fetuses. In 2000, the late John Fletcher noted “with sadness” that “a whole generation of researchers in reproductive medicine has been without federal support of fetal research and study of the beginning of embryonic development.”<sup>53</sup> Despite considerable advocacy for advancement of stem cell research, research on early embryos has had to progress without the funding—or oversight—of the federal government. President George W. Bush authorized research funding for a limited number of stem cell lines derived from human embryos before August 9, 2001.<sup>54</sup> In March 2009, President Obama issued an executive order rescinding Bush era limits and allowing research on stem cell lines created after that date.<sup>55</sup> Despite these steps forward, it remains the case that the federal government has not exerted influence through research funding to shape expectations about the appropriate translation of innovative ARTs into clinical practice.

Oversight will be addressed in greater depth in the following section; for the purposes of the present discussion, though, it is important to note the lack of federal funding as a factor leading to the definition of innovation in reproductive medicine as something other than research. New technologies are introduced into practice without having been scrutinized for

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52. Cynthia B. Cohen, *Unmanaged Care: The Need to Regulate New Reproductive Technologies in the United States*, 11 *BIOETHICS* 348, 357 (1997).

53. John C. Fletcher, *Deliberating Incrementally on Human Pluripotential Stem Cell Research*, in NAT'L BIOETHICS ADVISORY COMM'N, *ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH*, VOLUME II, E-1, E-42 (2000).

54. See NIH's Role in Federal Policy [Stem Cell Information], <http://stemcells.nih.gov/policy/NIHFedPolicy.asp> (last visited Apr. 1, 2010).

55. Exec. Order No. 13505, 74 Fed. Reg. 10667 (Mar. 9, 2009).

safety or efficacy. Independent clinics offering ARTs are not required to set up Institutional Review Boards (IRBs), nor are their innovative therapies subject to the Department of Health and Human Services (DHHS) regulations, which protect human subjects who participate in other areas of medical innovation. What evolved from the federal policy, Bonnicksen has noted, is the ironic fact that new reproductive technologies were “accepted as a clinical treatment but not as a subject of research.”<sup>56</sup>

#### 4. Economics

Economic forces have further encouraged the dissociation of ARTs and research. The high demand for these innovative reproductive services coupled with a void in federal funding and oversight has helped to make reproductive medicine more of a business than a research enterprise.<sup>57</sup> Further, dissociation from research serves the needs of those invested—both fiscally and professionally—in reproductive medicine. The market is based in large part on the therapeutic status of ARTs. Research questions will rest, in part, on questions about the safety and efficacy of interventions that are currently revenue-generating. Moreover, an absence of short-term and long-term data can be advantageous in a commercial environment in which economic returns are maximized by performing procedures. Among some commercially oriented health-care providers, there might be limited interest in developing data that could call into question the efficacy or safety of intervention or dramatic changes in practice.

Exacerbating matters further is the fact that ARTs are often not covered by insurance.<sup>58</sup> Restrictions on coverage are often based on the question of whether infertility should be considered an illness (despite the suffering it does clearly cause), and the claim that treatment is elective. The result is that any role insurance might play in encouraging evidence-based practice is minimized in the context of ARTs. Data indicates that insurance coverage has an impact not only on how many individuals have access to treatment, but on how

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56. ANDREA L. BONNICKSEN, *IN VITRO FERTILIZATION* 82 (1989).

57. See generally SPAR, *supra* note 9, at 195 (describing the baby making business as a growing business).

58. See Tarun Jain et al., *Insurance Coverage and Outcomes of In Vitro Fertilization*, 347 *NEW ENG. J. MED.* 661, 661 (2002) (stating that in the United States, in vitro fertilization is primarily a privately funded treatment).

fertility care is practiced. A landmark study in the *New England Journal of Medicine*, for example, found that state-mandated insurance coverage is associated with what might be concluded as more evidence-based and safer treatment: lower numbers of embryos transferred per cycle and lower numbers of pregnancies with three or more fetuses.<sup>59</sup> Limited insurance coverage contributes to the tendency for fertility care to operate more as a business than other areas of medicine, with market forces instead of regulatory oversight shaping the parameters of practice.

As a result of these social, clinical, political, and economic forces, reproductive medicine has come to occupy a space on the spectrum of research and therapy much closer to the latter, even at innovations' early stages. But even in circumstances when all would agree to its status as a research endeavor, current approaches to oversight are unlikely to afford research participants and beneficiaries the protections they deserve. While a full treatment of regulatory oversight for research is beyond the scope of this paper, the major challenges and opportunities for oversight of innovation in ARTs are considered.

#### B. REGULATION AND OVERSIGHT

In stark contrast to the complex regulatory structure regarding the oversight of research with human subjects in many fields of medicine, research and clinical treatment of infertility has been virtually unregulated. Instead “the regulation that exists is basically the result of inadvertent coverage of other areas such as abortion or fetal research legislation.”<sup>60</sup> An important factor in the promulgation of this regulatory void has of course been the aforementioned dissociation of innovation in reproductive medicine from experimentation. Further, though, four of the usual sources of regulatory control of innovation in medicine—federal funding of research activities, federal legislation, the FDA, and self-regulation by the industry—mark a minimally regulated space for innovation in ARTs.

Federal funding of research activities has been a major source of protection of human subjects in other fields of

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59. *Id.*

60. Patricia A. King, *Reproductive Technologies*, in 1 *BIOLAW: A LEGAL AND ETHICAL REPORTER ON MEDICINE, HEALTH CARE, AND BIOENGINEERING* § 7-3.5(d) (Childress et al. eds., 1986).

medicine. Researchers funded by the federal government are subject to the DHHS regulations.<sup>61</sup> On the other hand, reluctance to fund research on embryos and fetuses in the United States has resulted in the loss of what is otherwise an important source of oversight for innovative practices in fields other than reproductive medicine.<sup>62</sup>

Again, the story is one of protection gone awry. On July 25, 1975, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted conclusions and recommendations that formed the basis for regulations that the U.S. Department of Health, Education, and Welfare (DHEW) issued later that year in research involving fetuses, pregnant women, and embryos for human *in vitro* fertilization.<sup>63</sup> Known as Subpart B of 45 C.F.R. 46, the regulations aimed to create further protections for these particular individuals when subjected to federally funded research activities.<sup>64</sup>

As structured, the regulations have served not to protect these “vulnerable” populations, but rather to thrust the activities in which they have been involved out of the regulatory purview of the DHHS regulations. Research in IVF has never been eligible for federal funding. Subpart B created a *de facto* moratorium on federal funding of IVF until an “ethics advisory board” (EAB) could make recommendations to the Secretary of the DHEW regarding “the acceptability from an ethical standpoint” of a project involving research in this area.<sup>65</sup> It was not until September of 1978, stimulated by a

61. See 45 C.F.R. § 46.101–103 (2009).

62. See RONALD M. GREEN, THE HUMAN EMBRYO RESEARCH DEBATES: BIOETHICS IN THE VORTEX OF CONTROVERSY 15 (2001); Arthur L. Caplan, Letters, *Needed: A Modest Proposal*, 37 HASTINGS CENTER REP., Nov. 2007, at 4–11; The Inst. for Sci., Law, and Tech. Working Group, Ill. Inst. of Tech., *ART into Science: Regulation of Fertility Techniques*, 281 SCI. 651, 651–52 (1998).

63. THE NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMED. AND BEHAVIORAL RESEARCH, RESEARCH ON THE FETUS, REPORT AND RECOMMENDATIONS (1975), available at [http://bioethics.georgetown.edu/pche/reports/past\\_commissions/research\\_fetus.pdf](http://bioethics.georgetown.edu/pche/reports/past_commissions/research_fetus.pdf).

64. 45 C.F.R. § 46.201–207 (2009).

65. See 45 C.F.R. § 46.207(b) (2009); see also ETHICS ADVISORY BD., DEPT. OF HEALTH, EDUC., AND WELFARE, REPORT AND CONCLUSIONS: HEW SUPPORT OF RESEARCH INVOLVING HUMAN *IN VITRO* FERTILIZATION AND EMBRYO TRANSFER 1 (1979), available at [http://bioethics.georgetown.edu/pche/reports/past\\_commissions/HEW\\_IVF\\_report.pdf](http://bioethics.georgetown.edu/pche/reports/past_commissions/HEW_IVF_report.pdf) [hereinafter EAB SUPPORT OF *IN VITRO*].

funding request (already approved by a study section) from Pierre Soupart of Vanderbilt, that the Secretary directed the EAB to formulate recommendations for research involving IVF.<sup>66</sup> Dr. Soupart's goal had been to fertilize 450 eggs and study them to see whether the IVF process caused any chromosomal damage.<sup>67</sup> In March 1979 the EAB submitted a report recommending approval for federal funding of research on the safety and efficacy of IVF and embryo transfer and the study of spare, untransferred embryos.<sup>68</sup> However, no Secretary of DHEW or DHHS ever approved the recommendations, and DHEW Secretary Patricia Harris allowed the EAB charter to lapse in 1980 when its funding expired.<sup>69</sup> Although many efforts were made in the 1980s to reinstate the EAB, no federal action was ever taken.<sup>70</sup> In 1988, the Office of Technology Assessment reported that the effect of the moratorium on federal funding was "to eliminate the most direct line of authority by which the Federal Government can influence the development of both embryo research and infertility treatment so as to avoid unacceptable practices or inappropriate uses."<sup>71</sup>

The Revitalization Act of 1993 ended the *de facto* moratorium on research on IVF by nullifying the mandate that the EAB review any application or proposal for funding before its approval.<sup>72</sup> Subsequently, NIH director Harold Varmus established the Human Embryo Research Panel to determine which projects involving human embryos should be ethically acceptable for federal funding.<sup>73</sup> Among the most controversial aspects of the report was the recommendation that it might be ethical to fund research projects in which human embryos are created solely for research purposes. Before the NIH could

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66. EAB SUPPORT OF *IN VITRO*, *supra* note 65, at 1.

67. See Anne Taylor Fleming, *New Frontiers in Conception: Medical Breakthroughs and Moral Dilemmas*, N.Y. TIMES, Jul. 20, 1980, at 48.

68. See ETHICS ADVISORY BD., US DEPT OF HEALTH, EDUC., & WELFARE, REPORT AND CONCLUSIONS: HEW SUPPORT OF RESEARCH INVOLVING HUMAN IN VITRO FERTILIZATION AND EMBRYO TRANSFER 104 (1979)

69. Joseph Palca, *Capital Report: A Word to the Wise*, 24 HASTINGS CENTER REP., Mar.-Apr. 1994, at 5 (1994).

70. See Fletcher, *supra* note 53, at E-11.

71. OFF. OF TECHNOLOGY ASSESSMENT, U.S. CONG., INFERTILITY: MEDICAL AND SOCIAL CHOICES 179 (1988), available at <http://www.fas.org/ota/reports/8822.pdf>.

72. National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43, 113.

73. See Meeting of Panel/Request for Public Comment, 59 Fed. Reg. 28,874, 28,875 (June 3, 1994).



respond, President Clinton declared that federal funds should not be allocated for the creation of embryos for research purposes.<sup>74</sup> Varmus subsequently decided to accept the Panel's recommendations not proscribed by the President's declaration,<sup>75</sup> but again a window of opportunity was quickly shut. In 1996 and each year subsequently, Congress has attached a rider to the DHHS appropriations bill (the Dickey-Wicker Amendment), stating that no funds could be appropriated for any project involving "1) the creation of a human embryo or embryos for research purposes; or 2) research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* under 45 C.F.R. 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 USC 289g(b))."<sup>76</sup> Thus the assisted reproductive technologies have progressed without federal funding, and the human subjects participating in these innovative technologies have not been protected by federal regulations that apply to other fields of medicine.

Given federal funding restrictions, the curious evolution of ICSI begins to make more sense. Because scientifically rigorous development and refinement of ICSI would have involved the creation, destruction, and discarding of embryos, research involving this technique would not have been eligible for federal funding. As such, the technology advanced rapidly with neither federal funding, nor the scientific scrutiny or human subjects' protections that accompany it.

Some of the industry's leaders have argued, conversely, that the fertility industry is highly regulated,<sup>77</sup> and point to three sources of regulation in particular. First, they cite existing legislation, including voluntary reporting requirements for outcomes of fertility treatment. In 1992, the Fertility Clinic Success Rate and Prevention Act<sup>78</sup> set forth a requirement that

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74. Statement of Federal Funding of Research on Human Embryos, 30 WEEKLY COMP. PRES. DOC. 2459 (Dec. 2, 1994).

75. J.C. Fletcher, *Ethics and Society: U.S. Public Policy on Embryo Research: Two Steps Forward, One Large Step Back*, 10 HUMAN REPRODUCTION 1875, 1875 (1995).

76. 1 NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH 35 (1999).

77. Robert W. Rebar & Alan H. DeCherney, *Assisted Reproductive Technology in the United States*, 350 NEW ENG. J. MED. 1603, 1604 (2004).

78. See 42 U.S.C. § 263a-1 (2006).

the CDC develop model standards for the state certification of embryo laboratories. It also required the CDC to publish pregnancy success rates for ART procedures carried out in fertility clinics in the United States.<sup>79</sup> The first report was issued in December of 1997 and was based on data from 1995.<sup>80</sup> While an improvement over the regulatory void, the legislation is limited with regard to the question of research regulation. Participation in the program is voluntary without penalty to clinics for failure to report. More to the point, the publication of success rates is directed more at infertile patients as consumers than as subjects of research. It serves to catalog the practices and pregnancy rates of the majority of centers in the United States; patients can compare and contrast centers to help decide where to gamble substantial financial and emotional resources in their pursuit of pregnancy and childbearing. Guidelines for the introduction of new methods, informed consent and follow-up of long-term data are not addressed in the 1992 legislation.

Next, industry leaders cite the reach of the FDA as a source of regulation. For one, ART laboratories, which handle human tissues, are subject to inspection. But also, the agency's role in regulating use of innovative techniques has evolved, in particular in response to a technique known as ooplasm transfer, in which the ooplasm from a woman's egg is injected into the ooplasm of another woman whose embryos previously failed to develop. Fetuses conceived with this technique were found to have Turner syndrome, a relatively rare sex chromosome abnormality, raising familiar worries about the rapid integration of techniques into practice without adequate preliminary work.<sup>81</sup> The FDA "notified researchers that it would require an IND" before the technique could be used again in humans, which essentially "amounted to a clinical hold" on the procedure.<sup>82</sup> The story of ooplasm transfer, however, is a rare case of discretionary judgment by the FDA in a field it has tended to regard as beyond its purview.

And finally, industry leaders cite professional guidelines, and the usefulness of self-regulation. In 1986, the president of

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79. *Id.*

80. See Isabella A. Danel et al., *1995 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Report*, 7 J. WOMEN'S HEALTH 301, 301 (1998).

81. Susan M. Hawes et al., *Ooplasmic Donation in Humans: The Potential for Epigenic Modifications*, 17 HUM. REPROD. 850, 851 (2002).

82. Bonnicksen, *supra* note 51, at 75.

the American Fertility Society (now the American Society for Reproductive Medicine, ASRM) first appointed an Ethics Committee, representing professionals in law, bioethics, and reproductive medicine.<sup>83</sup> The committee has considered, on an ongoing basis, ethical issues which arise in the care of individuals with infertility. While the reports address important and clinically relevant issues, they fall short of providing adequate oversight for the protection of participants in innovative procedures. First of all, following the guidelines is voluntary, as adherence to the guidelines is not required for professional certification.<sup>84</sup> Second, the guidelines have tended to be “more descriptive of current practice than normative”<sup>85</sup> though some recent reports are directive.<sup>86</sup> Third, the guidelines are directed toward the infertility profession and do not have input from the public nor from disciplines outside of law, medicine, and bioethics, and so even if enforceable, these guidelines would not incorporate the comprehensive input which these pressing social issues deserve.

The U.S. approach to regulation of innovative technologies stands in contrast to that of many other countries that regulate the movement of innovative technologies from laboratory to clinic.<sup>87</sup> While a comprehensive survey of other nations’ policies is outside the scope of this manuscript, a brief review places the U.S. approach in context. Since 1998, the International Federation of Fertility Societies (IFFS) has surveyed a growing number of principal sovereign nations across the world about

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83. See, e.g., Stuart F. Spicker, *Overview of the Reports of the Ethics Committee of the American Fertility Society*, 14 J. MED. & PHIL. 477, 477 (1989) (“In September 1986, the Ethics Committee of The American Fertility Society (AFS) issued its initial report.”).

84. American Society for Reproductive Medicine, Practice Guidelines, [http://www.asrm.org/Guidelines\\_for\\_Practice/](http://www.asrm.org/Guidelines_for_Practice/) (last visited Apr. 22, 2010) (“These guidelines have been developed to assist physicians with clinical decisions regarding the care of their patients. They are not intended to be a protocol to be applied in all situations. . . . [A] [g]uideline presents a recommended approach to evaluation or treatment but is not intended to describe the only approved standard of practice or to dictate an exclusive course of treatment.”)

85. Cohen, *supra* note 52.

86. See, e.g., Ethics Comm. of the Am. Soc’y of Reprod. Med., *Donating Spare Embryos for Stem Cell Research*, 91 FERTILITY AND STERILITY 667, 667–70 (2009).

87. Lori P. Knowles, *The Governance of Reproductive Technology: International Models*, in REPROGENETICS: LAW, POLICY, AND ETHICAL ISSUES 127 (Lori P. Knowles & Gregory E. Kaebnick eds., 2007).

surveillance and oversight of ARTs.<sup>88</sup> According to the 2007 report, twenty-nine of fifty-seven nations surveyed have legislation regarding ARTs. The United States was one of seventeen to have guidelines; eleven countries reported neither statutory regulations nor voluntary guidelines.<sup>89</sup> The authors of the report noted that laws and guidelines of all countries were markedly divergent and that only three countries consider the regulatory situation to be “satisfactory.”<sup>90</sup>

Among those is Great Britain, whose Human Fertilisation and Embryo Authority (HFEA) is often considered exemplary, though commentators often raise concern about how such an Authority would function in the U.S. political context.<sup>91</sup> The HFEA was established in August of 1991 by the Human Fertilisation and Embryology Act. The recommendation came from a 1984 report of the Committee of Inquiry into Human Fertilisation and Embryology (called the “Warnock” report).<sup>92</sup> In order to protect society “from its real and proper fear of a rudderless voyage into unknown and threatening seas,”<sup>93</sup> the Warnock report recommended a statutory licensing authority to regulate the research and practice of new reproductive technologies.<sup>94</sup> Among the HFEA’s many functions are licensure and monitoring of clinics that carry out IVF, donor insemination (DI), and human embryo research.<sup>95</sup> Every clinic in the UK which carries out these activities is *required by law* to be licensed by the HFEA.<sup>96</sup> The HFEA also has a data register containing details of the outcomes of licensed treatments and patient characteristics in the UK.<sup>97</sup> Importantly, in addition to pregnancy rates (which are

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88. Howard W. Jones, Jean Cohen, Ian Cooke, and Roger Kempers, *IFFS Surveillance 2007*, 87 FERTILITY & STERILITY S1, S1–67 (2007).

89. *Id.*

90. *Id.* at S8.

91. John Robertson, *The Virtues of Muddling Through*, 37 HASTINGS CENTER REP., JULY–AUG. 2007, 26–28.

92. MARY WARNOCK, A QUESTION OF LIFE: THE WARNOCK REPORT ON HUMAN FERTILISATION AND EMBRYOLOGY (1985); HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY, ABOUT THE HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY 2 (2009), *available at* [http://www.hfea.gov.uk/docs/About\\_the\\_HFEA.pdf](http://www.hfea.gov.uk/docs/About_the_HFEA.pdf) [hereinafter ABOUT HEFA].

93. *Id.* at 100.

94. *Id.* at 74.

95. See Human Fertilisation & Embryology Authority, Who We Are & What We Do, Our Role as Regulator, <http://www.hfea.gov.uk/135.html> (last visited Apr. 18, 2010).

96. ABOUT HEFA, *supra* note 92, at 3–6.

97. *Id.* at 8, 15.

catalogued on a voluntary basis in the US), the HFEA collects data about developmental defects and syndromes that result from these procedures.<sup>98</sup> The HFEA also regulates research involving human embryos, and no new technique can be applied in humans without the approval of the HFEA.<sup>99</sup>

Harvard law professor Elizabeth Bartholet contrasts the activities of other countries with the situation in the United States: "This country is the only country in our technological position that hasn't, as a society, faced up to the various social and ethical issues involved in this technology."<sup>100</sup> Individuals in other countries have recognized the permissive approach in the United States; some have in fact have seized on the lack of regulations here as a means to overcome barriers they have faced in their own countries to ethically concerning technologies.<sup>101</sup> Reports have highlighted the United States as a "trade center" for reproductive and genetic technologies, drawing customers whose own countries ban given procedures. In contrast to the problematic efflux of ethically questionable research in other areas of medicine, the United States is seen among foreigners as a land of opportunity for the clinical application of novel reproductive procedures of unproven safety and unexamined societal import.

### III. ETHICAL AND POLICY ISSUES

As a result of the clinical and (lacking) regulatory structure in the United States upon which innovation in reproductive medicine is undertaken, several ethical and policy issues have surfaced. As intimated throughout the discussion thus far, new reproductive technologies raise at least three problems: 1) rapid introduction and integration of new technologies into clinical practice without a systematic way to insure that innovative therapies are reviewed prior to clinical application, 2) inadequate informed consent, and 3) lack of uniform standards for collection of data and surveillance of outcomes. The

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98. HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY, HUMAN RESEARCH IN THE UK 3-8 (2006/2007), *available at* [http://www.hfea.gov.uk/docs/HFEA\\_Human-Embryo-Research-06-07.pdf](http://www.hfea.gov.uk/docs/HFEA_Human-Embryo-Research-06-07.pdf).

99. *Id.* at 6.

100. ANDREWS, *supra* note 2, at 221.

101. *See, e.g.*, Alice Fishburn. U.S. Clinic Offers British Couple the Chance to Choose the Sex of Their Child, *TIMES ONLINE*, August 22, 2009, [http://www.timesonline.co.uk/tol/life\\_and\\_style/health/article6805880.ece](http://www.timesonline.co.uk/tol/life_and_style/health/article6805880.ece) (last visited May 6, 2010).

acceleration of science has made the laissez-faire approach to progress in reproductive medicine a subject of even greater urgency than it had been in previous years, when other innovative techniques set the stage of a similar debate. This mounting urgency becomes clear upon further consideration of the three problems which tend to characterize innovation in reproductive medicine.

#### A. PREMATURE INTEGRATION INTO PRACTICE

The first problem associated with reproductive medicine is that innovation is often characterized by rapid integration of new technologies into clinical practice without scientifically rigorous safety or efficacy data. Lori Andrews quoted one infertility doctor as saying: "We go from mindside to bedside in two weeks."<sup>102</sup> As discussed in the introduction, ICSI became standard practice in the vast majority of U.S. infertility clinics over the course of less than ten years. After only one year of clinical experience in the U.S. and in the absence of any long term data, the Practice Committee of the American Society for Reproductive Medicine recognized ICSI as clinical practice, stating "[s]everal recent independent studies have demonstrated the efficacy and short term safety of ICSI. Thus, its use for the treatment of male factor infertility is no longer considered experimental."<sup>103</sup> The procedure is now promoted, billed, and treated as standard therapy despite the fact that safety data is just now emerging. There is no regulatory framework which requires evidence of basic scientific merit, clinical benefit, or a favorable risk/benefit ratio before these new techniques can be integrated in to clinical practice.

#### B. INFORMED CONSENT

The second problem concerns the adequacy of informed consent. In a 1996 resolution, a joint council of the American Medical Association (AMA) issued a statement that informed consent to ARTs is often inadequate and inasmuch as it is, "subtle deception."<sup>104</sup> Similarly, the New York State Task Force

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102. Lori B. Andrews, *We Need Regulation of Reproduction*, in CLONING: FOR AND AGAINST 180 (M. L. Rantala & Arthur J. Milgram eds. 1999).

103. AM. SOC'Y FOR REPRODUCTIVE MED., PRACTICE COMMITTEE STATEMENT 2 (1994).

104. AM. MED. ASS'N COUNCIL ON ETHICAL & JUD. AFF. & COUNCIL ON SCI. AFF., ISSUES OF ETHICAL CONDUCT IN ASSISTED REPRODUCTIVE TECHNOLOGY 2 (1996), *available at* <http://www.ama-assn.org/amal/pub/upload/mm/369/70b.pdf>.

on Life and the Law studied the medical literature, consent forms used by practitioners in New York State, and interviewed patients and practitioners, and concluded, “There is considerable evidence that physicians provide incomplete or misleading information about benefits and risks, particularly the risks associated with multiple gestation,” and that “New York should enact legislation establishing minimum standards for obtaining informed consent to ARTs.”<sup>105</sup>

The context of reproductive medicine certainly exacerbates challenges to informed consent. Intense media attention, hopeful couples, and optimism on the part of physicians all create challenges to the adequacy of even the most carefully worded and exhaustive informed consent process. Furthermore, the commercial backdrop of ARTs may incline some providers to minimize risks and encourage treatment given financial incentives to treat. Given this enthusiasm, it can be unclear to participants just how experimental particular techniques are, or—given positive connotations of innovation—what the risks of innovative therapeutics might be.

But even when risks are known and communicated, patients hoping for a baby may discount the risks due to hopefulness, magical thinking, or cognitive challenges known to limit our ability to predict future emotional states.<sup>106</sup> Indeed, patients have described, in retrospect, the difficulty they encountered imagining how they would dispose of spare frozen embryos in advance of fertility treatment, reflecting the challenges of projecting future preferences.<sup>107</sup> Furthermore, fertility patients’ decisions about treatment may also simply be more strongly influenced by the potential for treatment success (i.e., a ‘take home baby’) than by risks to themselves or to future offspring.<sup>108</sup> In other words, they may find real risks to

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105. TASK FORCE ON LIFE & THE LAW, N.Y. STATE, EXECUTIVE SUMMARY OF THE TASK FORCE ON LIFE AND THE LAW, <http://www.health.state.ny.us/nysdoh/taskfce/execsum.htm> (last visited Apr. 22, 2010).

106. See generally Jodi Halpern & Robert M. Arnold, *Affective Forecasting: An Unrecognized Challenge in Making Serious Health Decisions*, 23 J. GEN. INTERNAL MED. 1708 (2008) (discussing “affective forecasting” and its implications for those facing health decisions).

107. Anne Drapkin Lyerly et al., *Fertility Patients’ Views About Frozen Embryo Disposition: Results of a Multi-Institutional U.S. Survey*, 93 FERTILITY & STERILITY 499, 502 (2010).

108. G. S. Scotland et al., *Safety Versus Success in Elective Single Embryo Transfer: Women’s Preferences for Outcomes of In Vitro Fertilisation*, 114

themselves and their babies as acceptable given the alternative of having no baby at all. And finally, the lack of information about outcomes of new techniques means patients have a limited basis upon which to decide whether to engage in the procedures, calling into question the validity of consent to participate in novel ARTs.

### C. SURVEILLANCE

The third problem associated with current approaches to innovation in reproductive medicine is the lack of uniform standards for collection of data and surveillance of outcomes. While the CDC registry reports pregnancy rates at participating infertility centers, there is no coordinated registry which reports any *health outcomes* in children or women exposed to new reproductive technologies in the United States. The data regarding outcomes of children conceived by ICSI were collected in Belgium and Australia<sup>109</sup>—ICSI children in the United States are not followed. Similarly, questions about links between fertility treatment and breast and ovarian cancer as well as concerns about long term cardiovascular risk in women who have conceived with ARTs have both emerged from retrospective data rather than carefully crafted surveillance. The failure to follow women prospectively has resulted in at best incomplete and potentially misleading information for patients considering ARTs. Furthermore, long term outcomes of these procedures, such as the reproductive health of children created by assisted conception are only just becoming measurable. In 1999, Louse Brown's sister Natalie became the first "test-tube baby" to bear a child on her own.<sup>110</sup>

## IV. MOVING FORWARD

These three ethical challenges—rapid introduction of new procedures without adequate evidence of safety or efficacy, inadequate informed consent, and lack of uniform standards for surveillance of outcomes—present a set of issues of critical

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BRITISH J. OBSTETRICS & GYNAECOLOGY 977, 978 (2007).

109. A. Van Steirteghem et al., *Follow-up of Children Born After ICSI*, 8 HUMAN REPRODUCTION UPDATE 111 (2002); Michèle Hansen et al., *The Risk of Major Birth Defects after Intracytoplasmic Sperm Injection and in Vitro Fertilization*, 346 NEW ENG. J. MED. 725 (2002); see also *Genetic Concerns over Fertility Treatments*, BBC NEWS, Dec. 15, 1998, <http://news.bbc.co.uk/2/hi/health/235419.stm> (last visited Apr. 18, 2010).

110. Carey Goldberg, *Just Another Girl, Unlike Any Other*, N.Y. TIMES, Oct. 27, 1999, at A16.



importance to the public and suggest a pressing need for a better approach. The decentralized and incremental policy around regulation of assisted reproductive policies will continue to generate inquiries and inspire debate. The correct policy for regulation—of practice and of innovation—has yet to be agreed upon. But critically, moving forward policymakers should attend to the morally and scientifically important distinctions between research and practice. The failure to do so in the past—on the part of physicians, scholars and policymakers alike—has had serious consequences. The challenges of regulating *innovation* in ARTs are distinct from those of regulating the *practice* of ART and need their own solutions. Fortunately, some initial approaches to remedying problems emerging from the lack of oversight are potentially straightforward.

First, funding is needed for research on ARTs—both because it will generate more information needed for the informed consent process and because it opens the door to regulation by the funding organization. After a decade of advocacy by scientists and health groups, access to federal funding for research on stem cell lines has recently become available (and regulations for such research developed). Yet funds for research on IVF techniques (which cross many of the same moral chasms) has not materialized, due in part to the ongoing force of the Dickey-Wicker Amendment.<sup>111</sup> Efforts to restrict funding for research have meant that innovation has occurred in a clinical setting without the requirements for informed consent or oversight usually afforded to research. According to the authors of the 2008 Cochrane review of evidence about the effectiveness of ARTs, “despite the large emotional and economic burden resulting from infertility, there is relatively little high-quality evidence to support the choice of specific interventions. Removing barriers to conducting appropriately designed studies should be a major policy goal.”<sup>112</sup>

Second, data is needed on health implications of ARTs for women and children. One approach would be to expand requirements for reporting to include more detailed information about pregnancy outcomes and longer term health

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111. See discussion *infra* note 76.

112. EFFECTIVENESS OF ASSISTED REPRODUCTIVE TECHNOLOGY, *supra* note 32, at v.

outcomes for both children and the women who undergo ARTs. Clearly this would present challenges since the fertility clinics that report to the CDC are not likely to routinely collect detailed information about obstetrical or long term outcomes, as patients are generally transferred to obstetricians once pregnancy is established. The challenges are clearly not insurmountable, as small strides toward collecting more complete pregnancy outcome data have been made. For instance, the CDC recently added a requirement to report singleton live births as a separate measure, since multiple gestations have a higher risk profile (for women and children both) compared to singleton births.<sup>113</sup> There may be other approaches to collecting these data as well, particularly observational studies of women and children during and after pregnancy. Coauthors and I have argued elsewhere that the U.S. National Children's Study, which plans to enroll 100,000 women prior to or in the first trimester of pregnancy and follow them and their children for 21 years has the potential to be a valuable source of information on the impact of IVF, particularly if maternal outcomes of pregnancy are added.<sup>114</sup>

Third, requirements for informed consent should be both clarified and standardized. They should include guidance about the distinct differential requirements for consent to participating in research versus consent to participating in clinical practice that necessarily includes inadequately tested though standard procedures. The practice committees of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology have made important progress, but because they identify "elements to be considered" in informed consent,<sup>115</sup> the guidelines are neither enforceable nor uniformly followed.<sup>107</sup> While progress has been made in describing requirements for informed consent for human oocyte, embryo, and embryonic stem cell research aimed specifically at stem cell transplantation for degenerative diseases (in other words, non-reproductive use of gametic or embryonic tissue),<sup>116</sup> far less attention has focused on

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113. 2006 ASSISTED REPRODUCTIVE TECHNOLOGY SUCCESS RATES, *supra* note 6, at 66, 67.

114. *The National Children's Study*, *supra* note 47.

115. Practice Comm. of the Am. Soc'y for Reproductive Med. & the Practice Comm. of the Soc'y for Assisted Reproductive Tech., *Elements to be Considered in Obtaining Informed Consent for ART*, 86 FERTILITY & STERILITY S272 (Supp. 4 2006).

116. Bernard Lo et al., *Informed Consent in Human Oocyte, Embryo, and*

requirements for informed consent for the therapeutic advancement of fertility that may likewise involve embryo manipulation or destruction.

Finally, while it is critical to mark the dividing line between innovation and practice in conversations about ethics and policy, there is a different dividing line whose blurring or erasure may to prove beneficial. In contrast to those who argue that the scope of conversation about regulation should be limited to research on embryos and fetuses that are outside a woman's body,<sup>117</sup> it can be argued the distinction complicates and potentially distorts ethical and policy analyses, and that more progress might be made with a more inclusive approach that encompasses reproductive care across prior to and following conception. The division of both clinical and moral labor (between fertility care and maternal-fetal medicine) can obscure or even worsen the situation when ethical questions regarding innovation are under consideration. For instance, at the clinical level, a longstanding disconnect between the goals of fertility care (pregnancy) and the goals of obstetrical care (singleton birth) has likely contributed to the high rates of multiple gestation. An important corrective has been reporting data about rates of singleton births (traditionally considered obstetrical data) in the CDC Fertility Clinic reports. Clearly, discontinuities in the care of patients and in conceptions of reproductive "success" in the application of new reproductive technologies have exacerbated the ethical and regulatory challenges in practice.

*This* point is not specific to practice: ethics and policy discussions about the regulation of innovation would benefit from a more unified approach that does not limit its purview to pre-gestation events. Section III.A highlights several challenges that have drawn both ARTs and maternal-fetal care outside the umbrella of research oversight and led to a paucity of safety and efficacy data: protectionist policies, tendencies to overlook the gestating or potentially gestating woman, regulatory loopholes specific to procedures, presumed therapeutic status associated with birth, and high consumer demand, to name a few. Given their shared genesis, the problems of innovation in pre- and post-conception reproductive

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*Embryonic Stem Cell Research*, 82 FERTILITY & STERILITY 559, 559 (2004).

117. Erik Parens & Lori P. Knowles, *Reprogenetics and Public Policy: Reflections and Recommendations*, in REPROGENETICS: LAW, POLICY, AND ETHICAL ISSUES 253, 256 (Lori P. Knowles & Gregory E. Kaebnick eds., 2007).

medicine are likely to have shared solutions. Finally, as we develop better understandings of epigenetics—of how environmental, nutritional and other factors before and during pregnancy can affect an offspring's health—recognition of the continuity of conception, gestation, birth, and long term health for women and children will be critical to coherent policy.

## V. CONCLUSIONS

The evolution of technology in reproductive medicine raises questions that are critical to patients and families today and which have profound implications for future generations. On the one hand, new techniques may provide relief of the suffering caused by infertility and the birth of children with preventable disabilities. On the other hand, innovation has ushered in problems with its progress. At the heart of the issue is their development in a social, clinical, political, and economic context that has distanced “innovation” from “experimentation.” The blurring of boundaries has resulted in a failure of oversight of human subjects research in reproductive medicine in the United States, and in the unwitting participation of thousands of individuals in experimental procedures without the protection of appropriately careful clinical investigation, informed consent, or data collection and reporting of outcomes. Though rich literature has recently developed about the merits and pitfalls of regulation for the practice of ARTs, much less discussion of late has focused on the process that has brought these ARTs to the bedside, despite the implications of unregulated innovation for the health of women and children. Better oversight of innovation in reproductive medicine is likely to result in safer technologies, better outcomes, and more informed decisions by men and women in the process of fertility care.