

Bad Drug Gone Good: An Explanatory Model for Drug Normalization

by

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ABSTRACT

Today in the U.S. the narrative of the “bad drug” has become quite a familiar account. There is an ever-growing collection of pharmaceutical products whose safety and efficacy has been debunked through the scandalous exposure of violations of integrity on the part of researchers, lapses in procedure and judgment on the part of the FDA, and reckless profiteering on the part of big pharma. However, a closer look reveals that the oversights and loopholes depicted in the bad drug narrative are not incidental failures of an otherwise intact, effective system. Rather, bad drugs, like good drugs, are a product of normal operations of the system; the same processes, actors, and influences manifest in both. The aim of this project is to shed light on these processes, actors, and influences at work in drug normalization by interrogating the peculiar case of the drug Lupron. Lupron exhibits all of the controversial features of the “bad drug” narrative but has remained an endorsed and embraced staple of the infertility industry. This contradiction situates Lupron to expose a number of the contingencies on which drug normalization rests more generally. In order to put forth an explanatory model for drug normalization, three such contingencies are described in detail for the case at hand: the nature of drug regulation, the structures and value that underpin the medical categorization of diseases, and the inextricability of post-medicine from the forces of industry. These contingencies provide some explanatory power for understanding not only the retention of Lupron but the ways in which all drugs are produced, validated, and perpetuated in a society.

DEDICATION

To my mom.

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INTRODUCTION

In recent years there has been no shortage of cases wherein the safety and efficacy of a drug has been called into serious question. Some examples include Paxil, the antidepressant that may lead to suicidal behavior¹; Belviq, the binge eating disorder pill with marginal efficacy and unanswered questions about its long-term effects²; Yaz, the birth control pill that has been linked to fatal cardiac and circulatory side effects but not yet recalled³; Vyvanse, the ADHD drug that recently received FDA approval to be marketed for weight loss⁴; Addyi, the “pink Viagra” marketed to improve female sex drive⁵; and countless others.

When the stories of these drugs are told, there are usually a few motifs that recur in the typical “bad drug” narrative. Pharmaceutical companies are cast as recklessly amoral profiteers. Doubt is sometimes cast on the way the FDA executed its discretion.

¹ Dobbs, David. “The Human Cost of a Misleading Drug-Safety Study.” *The Atlantic*, September 18, 2015. <http://www.theatlantic.com/health/archive/2015/09/paxil-safety-bmj-depression-suicide/406105/>.

² Beyerstein, Lindsay. “Fen-Phen All Over Again?” *Slate*, July 3, 2012. http://www.slate.com/blogs/xx_factor/2012/07/03/fda_approves_new_weight_loss_drug_belviq_is_this_fen_phen_all_over_again_.html.

³ Dearthoff, Julie. “Lawsuits Pile up over Popular Birth Control Pill.” *Chicago Tribune*, September 13, 2013. http://articles.chicagotribune.com/2013-09-15/health/ct-met-birth-control-risks-20130915_1_drospirenone-clots-pills.

⁴ Anderson, L. V. “This Drug for Binge-Eating Disorder May Be Shady. That Doesn’t Mean the Disease Isn’t Real.” *Slate*, February 25, 2015. http://www.slate.com/blogs/xx_factor/2015/02/25/binge_eating_disorder_vyvanse_may_not_be_the_right_treatment_but_the_problem.html.

⁵ Dobbs, David. “What the FDA’s Approval of ‘Pink Viagra’ Tells Us about the Problems with Drug Regulation.” *Vox*. Accessed October 4, 2015. <http://www.vox.com/2015/9/18/9333639/female-pink-viagra-fda-approved>.

Often there are revelations of fabricated evidence and concealed conflicts of interest. The affected patients are painted as victims duped by the powers that be.

By now the narrative is a little bit hackneyed. That is not to say that all of these characterizations aren't at least partly justified. But they don't seem to be sufficiently nuanced to depict what is really going on. The narrative is reductionist. It can get away with being reductionist because its focus is on the controversy and the wrong that has been committed. The key actors are usually rendered with clear-cut traits like malevolent intent, carelessness, or naivety. But these characterizations don't help us understand the complexity and fragility of the processes that really explain why questionable drugs are able to emerge, become popularly accepted, and achieve commercial success. All sorts of contingencies need to crystallize in order for this to happen. These crystallizations are the product of decisions that are made by individuals, communities, and organizations that hold discretionary power at different points in the process. Furthermore, all of these workings take place under a value system that is so basic and implicit to our understanding of the world that its significance is often taken for granted in the context of science and medicine.

This is all true not only of "bad drugs" that end up being challenged and/or recalled, but also those that turn out to be safe, effective, and beneficial. Drugs of both varieties are products of the same types of processes. "Bad drugs" are not exceptions to the rule, but rather one illustration of it. Maybe we would like to think of bad drugs as sporadic instances of Big Pharma successfully navigating a network of loopholes in an otherwise effective system of consumer protection in order to take advantage of

vulnerable patients. But in reality, these are the outcome of normal operations of the system. “Good drugs” traverse the same loopholes, travel the same paths, are driven by the same companies, and reach the same patient populations. The difference is that great deal of attention is given to the “bad drugs” because these are the cases where the system has ostensibly failed. There is little incentive to interrogate the operations of that system in cases where it produces desirable outcomes, even if those processes are the same ones that sometimes lead to undesirable outcomes. However, because drugs of all varieties have parallel explanatory backgrounds, a built understanding of how “bad drugs” come to be can help us understand the system at large.

The case of Lupron is intriguing because its story has all of the scandalous characteristics of the “bad drug” narrative, from a striking lack of evidence supporting its safety, to widespread accounts of devastating side effects, to devious and illegal business practices on the part its manufacturers; and yet, Lupron is not only systematically overlooked by regulatory overseers but heartily endorsed by the medical establishment. Indeed, Lupron is widely viewed as an *indispensable* component of standard *in vitro* fertilization (IVF) protocols. In this way it defies our expectations. This strange and compelling contradiction makes Lupron a good candidate for explanatory deconstruction in order to build an understanding of the processes that produce, legitimize, and normalize a drug. This project seeks to interrogate the contradiction given by the case of Lupron in order to expose and make sense of some of these processes.

Interrogating the case Lupron involves asking a series of related questions. First, what forces crystallized in order for Lupron to become recognized as the foremost drug

of its type? Similarly, what led drugs of this type to become critical to IVF? What contingencies explain the acceptance of IVF as an infertility treatment and, more generally, for the medical treatment of fertility to be in public demand? Furthermore, what players were active in all of these crystallizations? What discretion did those players exercise? In what sort of space were they operating and what values were implicit in that space? This line of questioning can, of course, be asked of any drug, whether good or bad. The case of Lupron does not encapsulate all of the complexities and dynamics required to explain the emergence and legitimization of every drug. But those processes that are at play in the case of Lupron are relevant to other drugs and their exposition can help make sense of drug normalization more generally. Thus, the goal of this analytical project is to point to certain social facts and in doing so articulate an explanatory model for how a particular pharmaceutical that complicates the good/bad drug dichotomy has become entrenched in a society. Addressing the aforementioned questions about Lupron in particular can help illuminate some of the broader institutional, economic, regulatory, and sociocultural configurations that underlie the production and consumption of drugs. Although it is not often acknowledged, all of these configurations are based in values. Things like markets, regulation and policy, and even medicine itself are all constructions of human origin and can be traced back to systems of values. Though these things are taken as given, in order to truly understand them and their outcomes it is important to not treat them this way and instead unpack their underlying values. By taking a hard look at these configurations and extracting their underlying values we can better grasp why they exist, how they dictate the actions of institutions and

individuals, and the types of relationships between different actors that they promote. This is important because in order to be able to say whether something—in this case, the structures and processes associated with drug normalization—is working as desired it of course must first be known how it works.

With these aims in mind, the subsequent discussion is organized as follows: in the Section I provide background information on the case study. I describe what the drug Lupron is, what it does, and why it is the source of some amount of controversy. In Section II, I offer historical context for the case study. I do this by providing an overview of the history of medical infertility treatment since the discovery of the fertilization event, with a special focus on the history of IVF. I also outline a history of Lupron since its entry into the drug market and discuss its confluence with the infertility industry. In Section III, I illustrate a typical scenario of a woman who is pursuing infertility treatment at an IVF clinic and the activities and interactions that comprise her experience. This seemingly banal, routine scenario becomes extraordinary when it is colored with the knowledge of Lupron as a “bad drug,” and thus paves the way for us to ask on what this scenario is contingent. In Section IV, I proceed to unravel this scenario to examine the converging forces and factors that allow it to take place. These are addressed in several sub-sections, including the sociocultural values that underpin reproduction, the privatized and technocratic landscape of the infertility industry, and the nature of the regulatory environment in which this is embedded. In Section V, I recap the key messages from my previous discussion in the form of set of contingencies that have allowed Lupron to take the course that it has taken. Together these contingencies represent an explanatory model

for the normalization of drugs more generally, regardless of whether they are good or bad.

SECTION I: BACKGROUND

Lupron is the brand-name version of the drug leuprolide acetate. Biochemically, leuprolide acetate is a gonadotropin-releasing hormone (GnRH) agonist. This means that the drug imitates the chemical structure of GnRH, a hormone responsible for triggering the production of testosterone and estradiol. These latter two hormones carry out variety of biochemical functions in the reproductive tissues of both men and women. By imitating GnRH Lupron serves to desensitize the body's GnRH receptors and therefore suppress the production of all downstream sex hormones.⁶ Thus, Lupron produces a variety of physiological consequences for both the male and female reproductive systems and is used in the treatment of disease states related to those systems.

Lupron was first introduced to the pharmaceutical market in 1985 when it received approval from the FDA as a palliative treatment for prostate cancer. Lupron's ability to suppress testosterone production proved (and continues to be) useful in slowing the growth rate of cancerous cells in the prostate. In the years since its introduction, Lupron's medical purview has expanded considerably from its modest beginnings as a palliative cancer care drug for men. Multiple dosage variations of Lupron have been introduced and its approved uses have expanded across the sexes and ages to include

⁶ Magon, Navneet. "Gonadotropin Releasing Hormone Agonists: Expanding Vistas." *Indian Journal of Endocrinology and Metabolism* 15, no. 4 (2011): 261–67. doi:10.4103/2230-8210.85575.

indications experienced by women, such as endometriosis and pre-operational fibroids, as well as precocious puberty in children.

Today, although Lupron is only officially approved for the aforementioned purposes, one of its most prevalent applications is its off-label use in the most popular form of infertility treatment: in vitro fertilization (IVF). In the context of IVF, Lupron serves to inhibit female ovulation and force the body into an artificial and temporary post-menopausal state.⁷ The subsequent withdrawal of Lupron and introduction of additional hormones to stimulate ovulation then encourages the release of many more eggs than is typical of a woman's average cycle. Such a surge in egg production is seen as desirable, especially from the standpoint of the infertility clinician, because the ultimate success rate of IVF can be maximized by harvesting as many eggs per cycle as possible. Lupron's application in IVF continues to expand in parallel to the infertility industry, despite the fact that it has not received FDA approval for this purpose. In fact, Lupron is officially *contraindicated* by the FDA for women who are or may become pregnant.⁸ Despite all of this, within the realm of assisted reproductive technology Lupron is considered an essential, indispensable component of the IVF process. Its use is at this point deeply entrenched in the norms and practices of the industry.⁹

⁷ U.S. Food and Drug Administration. "NDA 019732/S-037 Lupron Depot 7.5 mg (leuprolide acetate for depot suspension)." Reference ID: 2888059.

⁸ U.S. Food and Drug Administration. "NDA 019010/S-036 Lupron (leuprolide acetate) Injection." Reference ID: 2888059.

⁹ I use the term "entrenched" to indicate Lupron's largely unquestioned fixedness in IVF protocols. The fact that Lupron was the first drug of its type to enter the market and become widely used has led to this state of pervasive entrenchment. By entering on the ground floor of an industry that is based on technocratic and consumer-driven formulations of knowledge, Lupron developed a legacy of effectiveness that made it, in some sense, the "safest" choice for women pursuing IVF. It has become their best bet

On one hand, this is not at all surprising. Lupron is quite effective at accomplishing its role in IVF, which has become an increasingly reliable biotechnological solution to the problem of infertility. On the other hand, the pervasiveness and importance of Lupron in IVF seems somewhat extraordinary given the striking absence of evidence demonstrating its safety in this context as well as lack of approval from the FDA. In these ways and others, the story of Lupron presents some interesting revelations how knowledge becomes engrained and how standards are developed with regard to health, disease, and treatment. At the same time, the case demonstrates in a broad sense what is required for the successful validation and popularization of a health commodity like itself. The case of Lupron leads us to ask certain questions. In what ways does Lupron defy our expectations about the relationship between drug and disease? How does the case of Lupron unsettle our ideas about the role that knowledge plays in health? What does it reveal about the complex, market-driven relationship between pharmaceuticals, their indications, their regulators, and their patient consumers? And what does it show us about the essential ingredients for the production and commodification of health solutions? We can shed light on these questions by telling the story of Lupron and interrogating the dynamics that have carried it to proliferation in medicine and the infertility industry.

simply by being the known option. Although in an official sense very little is known about Lupron, its long-standing and wide application lead it to persistently overshadow alternative options about which even less is known. In this way the use of Lupron has crystallized into a norm of IVF practice.

SECTION II: THE CONVERGENT HISTORIES OF IVF AND LUPRON

In order to understand the nature of Lupron's role in infertility treatment, it is important to know something about its history as a pharmaceutical, as well as the history of IVF as a procedure. Both the drug product Lupron and the technique of IVF existed independent of one another before converging to become seamless components of today's most popular assisted reproductive technology. The story of their convergence into a medical solution for infertility provides context for unraveling the dynamics at play in this curious case.

The History of Infertility Treatment and in vitro Fertilization

The inability to bear children, or “involuntary childlessness,” has been considered problematic in one way or another (economically, socially, spiritually, etc.) by many societies around the world and across time. Depending on how these societies primarily conceptualized involuntary childlessness, its solutions have varied from adoption to religious rites to fashionable therapeutic measures such as sea bathing and consumption of dog meat.¹⁰ A full account of the many historical and cultural approaches to involuntary childlessness is beyond the scope of this project; it will suffice to remark that the inability to bear children is a status that has been culturally interpreted and problematized in many different ways. In the U.S. today, the dominant interpretation of involuntary childlessness is, for the most part, a strictly medical one. Consequently, it is

¹⁰ Greil, Arthur L. *Not yet Pregnant: Infertile Couples in Contemporary America*. New Brunswick [N.J.]: Rutgers University Press, 1991.

this interpretation that will be the focus of the forthcoming historical account of the relationship between infertility, IVF, and Lupron.

Interpretation of involuntary childlessness as the medical condition of “infertility” is a relatively recent historical development. The most basic piece of foundational knowledge leading to modern medical infertility treatment can be traced back to the mid-19th century, when it was recognized that conception results from the fertilization of an ovum with a sperm cell. A physiologically accurate understanding of conception was, until then, unprecedented. This knowledge paved the way for the identification of conditions that impeded fertilization as well as the development of medical techniques seeking to overcome those conditions. The most popular of these included artificial insemination and partial ovarian transplantations, both which were performed with very limited success during the early 20th century. Despite the meager success rates of these early infertility treatments, the domain pushed forward, carried partly by the impetus of popular demand by women who were involuntarily and unhappily childless.

The first U.S. infertility clinic was founded by gynecologist John Rock 1926 as part of the Free Hospital for Women in Baltimore. Shortly after came the seminal discovery that would come to revolutionize the treatment of infertility: the identification of the female sex hormones progesterone and estrogen in 1928 and 1929¹¹. The realization that hormones play a critical role in ovulation and pregnancy broadened the focus of infertility treatment, which had until this point been largely surgical in its approach. Acknowledgment of this biochemical dimension of fertility led to the

¹¹ “WGBH American Experience . Test Tube Babies | PBS.” *American Experience*. Accessed September 20, 2015. <http://www.pbs.org/wgbh/americanexperience/features/timeline/babies/>.

formation of new field known as reproductive endocrinology. Even today this field continues to serve as the primary medical specialization for addressing infertility.

It wasn't long before physicians began leveraging endocrinology in the realm of childbearing. In the early 1940s, doctors began prescribing the first synthetic estrogen, diethylstilbesterol (DES), to pregnant women. It was believed that this estrogen analog would prevent pregnancy complications and miscarriages, but in fact these alleged benefits were unsubstantiated and ultimately false. It was later discovered that DES causes a rare form of vaginal cancer in the children of women who had taken the drug while pregnant, and it was eventually recalled completely.¹² Thus, although endocrinology was a rapidly growing field during the early to mid-twentieth century, the case of DES suggests that the role played by hormones in pregnancy was still poorly understood at this time. It was not until several decades later that hormones were used in the capacity of infertility treatment. This can be at least partly explained by the persistent embrace throughout the 1950s of the misled notion that female infertility was strictly rooted in emotional problems. In the 1960s, however, the development of two particular pharmaceuticals demonstrated otherwise. Clomiphene citrate and human menopausal gonadotropin (hMG) were discovered to be effective at regulating the ovulatory cycle and thus presented a solution to infertility in cases where irregular ovulation or anovulation was the source of the problem. These two drugs represent the first truly reliable

¹² United States Department of Health and Human Services. Centers for Disease Control and Prevention. "DES History."

pharmaceutical solution for infertility.¹³ Clomiphene citrate and hMGs continue to play a major role in IVF to this day.

While great strides were made in understanding the biochemical dimensions of fertility during the early- to mid-twentieth century, surgical avenues of treatment were simultaneously (but separately) explored. Indeed, almost as soon as the mechanism of fertilization was discovered in 1878, scientists and physicians began to attempt to fertilize a variety of mammals' ova *in vitro* and produce embryos.¹⁴ In 1934, the *in vitro* fertilization and transplantation of rabbits' ova was first attempted by U.S. scientist Gregory Pincus. Although Pincus failed in his attempt, the implications of his work caused him to be publicly vilified, denied tenure, and dismissed from his position at Harvard University.¹⁵

Thus, it is clear that from the earliest stages of IVF, the U.S. presented an ideological backdrop that was hostile and unreceptive to the technology. While these ethical concerns deterred some scientists (such as the aforementioned Dr. John Rock), others continued their quest to achieve mammalian *in vitro* fertilization outside of the approval of the media and oversight bodies¹⁶. Over a hundred unsuccessful attempts to fertilize human ova were carried out over the course of the mid- to late-1940s, though

¹³ Greil, Arthur L. *Not yet Pregnant: Infertile Couples in Contemporary America*. New Brunswick [N.J.]: Rutgers University Press, 1991.

¹⁴ Bavister, B. D. "Early History of *in Vitro* Fertilization." *Reproduction* 124, no. 2 (August 1, 2002): 181–96. doi:10.1530/rep.0.1240181.

¹⁵ "American Experience | The Pill | People & Events: Gregory Pincus." Accessed September 30, 2015. http://www.pbs.org/wgbh/amex/pill/peopleevents/p_pincus.html.

¹⁶ Biggers, John D. "IVF and Embryo Transfer: Historical Origin and Development." *Reproductive BioMedicine Online* 25, no. 2 (August 2012): 118–27. doi:10.1016/j.rbmo.2012.04.011.

these experiments were performed with no intent to implant and engender pregnancy. Only in 1959 was it demonstrated for the first time in a rabbit model that in vitro fertilization of an egg and subsequent transplantation of the resulting embryo could lead to pregnancy, normal development, and live birth.¹⁷

This critical proof of concept demonstrating that the technology really could produce children was a major achievement that vitalized the field of IVF during a time when the establishment's ethical objections to reproductive technology were very strong. Pope Pius XII had officially condemned IVF in 1949 on the grounds that it violated God's natural order. In 1954, a court in Illinois ruled that children who were the result of artificial insemination by donor sperm were illegitimate in the eyes of the law¹⁸. Despite these and other condemnations by authorities, demand for IVF remained strong among communities of infertile couples, and research and development in the field pressed on.

In 1968, human ova were successfully fertilized *in vitro* for the first time by doctor Patrick Steptoe and embryologist Robert Edwards. This achievement was made possible in part by the development of laparoscopic surgical technique, which allowed for retrieval of fully mature eggs from the ovaries.¹⁹ Although no attempt was made to implant these embryos, this milestone reinforced assisted reproduction and infertility as a legitimate and lucrative medical subfield, as evidenced by the fact that the number of

¹⁷ Cohen, Jean, Alan Trounson, Karen Dawson, Howard Jones, Johan Hazekamp, Karl-Gösta Nygren, and Lars Hamberger. "The Early Days of IVF Outside the UK." *Human Reproduction Update* 11, no. 5 (September 1, 2005): 439–60. doi:10.1093/humupd/dmi016.

¹⁸ "WGBH American Experience . Test Tube Babies | PBS." *American Experience*. Accessed September 20, 2015. <http://www.pbs.org/wgbh/americanexperience/features/timeline/babies/>.

¹⁹ "WGBH American Experience . Test Tube Babies | PBS." *American Experience*. Accessed September 20, 2015. <http://www.pbs.org/wgbh/americanexperience/features/timeline/babies/>.

physician members of the American Fertility Society increased from 3,000 in 1968 to 10,000 in 1984.²⁰ However, at the same time that support was mounting in the medical community, a majority of Americans remained opposed to IVF.²¹

Even so, the number of infertile couples willing to subject themselves to experimental IVF attempts was in no short supply. In the U.S., the first attempt to implant a fertilized embryo into a woman was carried out by doctors William Sweeny and Landrum Shettles. Their patient was Doris Del-Zio who, after several unsuccessful reparative surgeries as well as several failed attempts at artificial insemination, was offered an opportunity to undergo IVF in 1973. Del-Zio underwent six months of treatment with fertility drugs before her eggs were surgically removed by Sweeny. Shettles then fertilized the eggs with sperm from Del-Zio's husband, unbeknownst to his superiors at Columbia-Presbyterian Hospital. When the chairman of the hospital, Raymond Vande Wiele, learned of the IVF attempt through Shettles' colleagues, he immediately terminated the incubation of the embryos, eliminating any possibility of implantation and pregnancy for Del-Zio. Vande Wiele did so on the grounds that Shettles' activities violated federal regulations, put the hospital at risk of losing funding, and put the hospital in a position of liability if the IVF attempt ended poorly. Ironically, the Del-Zios ended up suing both the hospital and Vande Wiele anyway for forcibly and

²⁰ Greil, Arthur L. *Not yet Pregnant: Infertile Couples in Contemporary America*. New Brunswick [N.J.]: Rutgers University Press, 1991.

²¹ Cohen, Jean, Alan Trounson, Karen Dawson, Howard Jones, Johan Hazekamp, Karl-Gösta Nygren, and Lars Hamberger. "The Early Days of IVF Outside the UK." *Human Reproduction Update* 11, no. 5 (September 1, 2005): 439–60. doi:10.1093/humupd/dmi016.

abruptly putting an end to the attempt²². The controversy was a major stumbling block in the course of IVF research in America and set the country back several years in its progress. Ultimately, the first successful IVF attempt was executed in England by doctors Edwards and Steptoe, who had been working for ten years on fertilizing a human egg *in vitro*. An embryo implanted in Lesley Brown became the first of many efforts to advance to pregnancy and eventually the much-anticipated live birth of Louise Brown, the first “test tube baby,” in 1978.

It is interesting to note that the first successful human IVF procedures did not involve pharmaceuticals in any way. Although Edwards and Steptoe had attempted to couple IVF with fertility drug therapy, their sustained lack of success led them to strip down their methods to a purely surgical procedure.²³ After the successful birth of Louise Brown from these surgical methods, Edwards and Steptoe continued to perform IVF in the same way, carrying out egg retrievals without any hormonal stimulation of the mother. Their methods carried a 6% pregnancy rate per cycle.²⁴ However, the low levels of egg retrieval and low pregnancy rate reflected in early IVF led investigators to return to an exploration of pharmaceuticals as a way to stimulate increased and predictable egg production. Human menopausal gonadotropins (hMGs), which had been used to

²² “WGBH American Experience . Test Tube Babies: First U.S. Test Tube Baby Attempt | PBS.” *American Experience*. Accessed October 1, 2015. <http://www.pbs.org/wgbh/americanexperience/features/general-article/babies-first-us-attempt/>.

²³ Biggers, John D. “IVF and Embryo Transfer: Historical Origin and Development.” *Reproductive BioMedicine Online* 25, no. 2 (August 2012): 118–27. doi:10.1016/j.rbmo.2012.04.011.

²⁴ Wang, Jeff, and Mark V Sauer. “In Vitro Fertilization (IVF): A Review of 3 Decades of Clinical Innovation and Technological Advancement.” *Therapeutics and Clinical Risk Management* 2, no. 4 (December 2006): 355–64.

modulate ovulation since the 1940s, were the drug of choice for this purpose. By 1983, researchers were reporting a 30% pregnancy rate per cycle as a result of the use of hMGs. In 1986, the first hMG drug product, Metrodin, was approved for use in the treatment of infertility in women suffering from polycystic ovarian syndrome.²⁵ Although hMGs greatly increased the success rate of IVF, 1 in 5 cycles stimulated with hMGs failed as a result of premature ovulation.²⁶ The answer to this problem came in 1984 in the form of a variety of drugs known as gonadotropin releasing hormone agonists (GnRH agonist). Prior to administering hMGs, a phase of treatment with GnRH agonists was implemented in order to place women's bodies in a state of artificial post-menopause. Arresting women's regular hormonal pathways effectively prevents premature ovulation up until the point when its administration is ceased, causing a deluge of eggs to be produced. Integration of GnRH agonists into IVF protocols increased resulting pregnancy success rate to as high as 55% as reported by some studies.²⁷ The first commercial GnRH agonist to be applied in this capacity was Lupron.

The History of Lupron

Lupron made its market debut in 1985 as the flagship product of Takeda Abbott Pharmaceuticals (TAP), a joint venture between the Japanese company Takeda Chemical

²⁵ U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.

²⁶ Elter, K., and L. R. Nelson. "Use of Third Generation Gonadotropin-Releasing Hormone Antagonists in in Vitro Fertilization-Embryo Transfer: A Review." *Obstetrical & Gynecological Survey* 56, no. 9 (September 2001): 576–88.

²⁷ Elter, K., and L. R. Nelson. "Use of Third Generation Gonadotropin-Releasing Hormone Antagonists in in Vitro Fertilization-Embryo Transfer: A Review." *Obstetrical & Gynecological Survey* 56, no. 9 (September 2001): 576–88.

Industries Limited and Abbott Laboratories in the U.S. Lupron's inaugural indication was its use in the palliation of advanced prostate cancer. For several years thereafter, prostate cancer remained the sole approved use of the drug. Despite the fact that it entered the market officially stamped as a palliative cancer drug for men, Lupron began converging on the women's infertility industry quite early on in its lifetime as a drug. This convergence is not surprising in light of the fact that GnRH agonists were being investigated (but not yet widely used) in the context of IVF years before Lupron even entered the drug market.²⁸ Driven by its capacity to dramatically increase the number of eggs generated in a cycle of IVF, Lupron rapidly pervaded the infertility industry and by 1989 was considered a virtually indispensable staple of IVF protocols.²⁹

Just as rapidly as Lupron rose in prevalence, so too did tensions arise between different stakeholders responsible for validation for the drug. In 1990 TAP was cited by the FDA for having “undertaken a deliberate campaign to promote this product [Lupron] for a wide range of unapproved uses,” especially through “a large number of detail representative visits to obstetricians and gynecologists.”³⁰ The scandal generated by TAP marketing Lupron, a prostate cancer drug, to OB/GYNs was soon resolved, however, when Lupron received approval for use in the treatment of endometriosis in 1990. With

²⁸ Porter, R.N, W Smith, I.L Craft, N.A Abdulwahid, and H.S Jacobs. “Induction of Ovulation for in-Vitro Fertilisation Using Buserelin and Gonadotropins.” *Lancet* 2, no. 8414 (1984): 1284–85. doi:10.1016/S0140-6736(84)92840-X.

²⁹ Martin, Mary C., Carolyn R. Givens, Eldon D. Schriock, Robert H. Glass, and Pramila V. Dandekar. “The Choice of a Gonadotropin-Releasing Hormone Analog Influences Outcome of in Vitro Fertilization Treatment.” *American Journal of Obstetrics and Gynecology* 170, no. 6 (June 1994): 1629–34. doi:10.1016/S0002-9378(94)70333-7.

³⁰ Feather, Kenneth R. *Notice of Adverse Findings*. Letter. From Food and Drug Administration. (accessed June 14, 2015).

the approval of Lupron for an indication related to the female reproductive system, suddenly the marketing of the drug to obstetricians and gynecologists a perfectly acceptable activity for TAP to undertake. Lupron was later also approved for the treatment of pre-operational uterine fibroids in 1995. Importantly, with these additional approvals, Lupron gained uninhibited access to the realm of women's healthcare, including fertility and reproduction.³¹ Lupron has also accrued one pediatric indication—precocious puberty—for which it was approved in 1993.

Since its introduction thirty years ago, a wide range of dosages of Lupron have been approved and marketed for different purposes. Presently the array of available Lupron products includes depot suspensions for subcutaneous injection ranging in concentration from 3.75 mg to 45 mg, as well as several generic formulations of leuprolide acetate.³² In more recent years, name-brand Lupron has changed proprietary hands on several occasions. In 2008, the TAP joint venture dissolved and Abbott laboratories retained the rights to produce and market Lupron. Three years later, Abbott Laboratories began restructuring in order to create a sub-branch of the company (known as AbbVie) that would be dedicated to pharmaceutical research. When the branches finalized their split in 2013 AbbVie retained the rights to Lupron.³³ Through these

³¹ Although obstetrics and gynecology are generally not the most prevalent specialty that carries out IVF procedures, they were (and continue to be) the primary gatekeepers of infertility diagnoses and patients' first point of access in pursuit of fertility treatment.

³² "Drugs@FDA: FDA Approved Drug Products." Accessed October 4, 2015. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=LUPRON%20DEPOT>.

³³ Cahill, Joe. "Abbott vs. AbbVie: Look Who's on Top Now." *Crain's Chicago Business*. Accessed June 11, 2015. <http://www.chicagobusiness.com/article/20150204/BLOGS10/150209918/abbott-vs-abbvie-look-whos-on-top-now>.

commercial maneuvers, Lupron has remained the largely unquestioned drug of choice for hormonal downregulation in IVF protocols.

Although there is no universally established regimen for the administration of Lupron during IVF cycles, the great majority of cycles today generally adhere to what is known as the “long Lupron” protocol.³⁴ In this method, an injection of one of the lower available doses of Lupron is self-administered for about 16 consecutive days, the latter half of which are coupled with the administration of a follicle stimulating hormone product before performing surgical retrieval of eggs.³⁵ To date, roughly 5 million children have been born to date as a result of IVF, thanks in part to (among other advances) the efficiency and optimization of egg production rendered by Lupron. Further, as IVF becomes more popularized and well-accepted, a larger number of babies are produced using IVF each passing year³⁶ (making up about 1.6% of the total annual births taking place in the U.S. as of 2013³⁷) and therefore the enormous market for Lupron continues to grow. To give a sense of the magnitude of this market, in 2012 (the most recent year

³⁴ Two other less-used but still common methods include the “microflare” protocol and the “antagonist” protocol. The microflare protocol is used in women who have experienced or are at risk for over-suppression and entails dilute injections of Lupron administered twice daily along with follicle stimulating hormone for approximately 8 days. The antagonist protocol is used in women who have experienced or are at risk for ovarian hyperstimulation and involves several doses of a GnRH antagonist (rather than an agonist like Lupron) at the end of about 8 days of follicle stimulation.

³⁵ Sherbahn, Richard. “In Vitro Fertilization, IVF – the Process and Procedures.” Advanced Fertility Center of Chicago. Accessed October 6, 2015. <http://www.advancedfertility.com/ivf.htm>.

³⁶ According to the Society for Assisted Reproductive Technology, in 2003, 82,930 cycles of IVF were performed in the U.S. with 23,706 of those resulting in live births. A decade later in 2013, these numbers had doubled to 165,172 cycles and 61,740 live births.

³⁷ Massy-Beresford, Helen. “What’s next for the World’s 5 Million IVF Babies?” *The Guardian*, November 23, 2014, sec. Society. <http://www.theguardian.com/society/2014/nov/23/whats-next-for-worlds-5-million-ivf-babies>.

for which data is available) a total of 128,628 cycles of IVF were performed.³⁸ If it is assumed that a Lupron-based protocol was used in even a mere 80% of these cycles, at an average cost of \$200 per regimen of the drug this would amount to a total market value of approximately \$20.6 million. Thus, Lupron has developed a highly lucrative market that promises to expand further with the continued growth of the infertility industry.

The “Bad Drug” Narrative Takes Shape

“Scientifically, there are some unanswered questions about the long term consequences those drugs might have on women. There are questions about whether they lead to the production of unhealthy eggs, and whether they pose a cancer risk to the mother. That’s an area that we...hope to examine.”³⁹ – Kathy Hudson

For all the arguable good it has done in enabling the existence of millions of human beings, since the early-1990s Lupron has become embroiled in a mounting controversy concerning its use in IVF. Indeed, over the years Lupron has accumulated all of the marks of the conventional “bad drug” narrative, not the least of which is the fact that Lupron has never been approved by the FDA for use in IVF protocols. Even more outwardly shocking than this is the fact that there have been remarkably few attempts to investigate its safety and efficacy in this context. As of October of 2015 only one clinical trial on the safety and efficacy of Lupron in the context of IVF has been performed, completed, and reported results, despite the fact that Lupron has now been used to facilitate IVF for some 30 years. This absence of evidence is starkly contrasted to the

³⁸ Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. “2012 Assisted Reproductive Technology Fertility Clinic Success Rates Report.” U.S. Department of Health and Human Services (Atlanta, GA, 2014).

³⁹ “The Future of Research and Regulation for Infertility Treatments.” *Popular Science*. Accessed July 26, 2015. <http://www.popsci.com/scitech/article/2003-02/future-research-and-regulation-infertility-treatments>.

dozens of clinical trials that have investigated the role of Lupron in the treatment of its original introductory indication of prostate cancer.

In defense of Lupron's use in IVF protocols, one might note that clinical trials were carried out to investigate its safety and efficacy in the treatment of indications related to the female reproductive system (i.e., endometriosis and fibroids). Such a demonstration of Lupron's safety and effectiveness in women for these indications might normally provide reassurance that its off-label use by women undergoing IVF is equally safe. However, for several reasons this evidence has done little to temper the controversy of Lupron's use in IVF. First, the favorable conclusions produced by the clinical trials of Lupron in endometriosis and fibroids remain questioned. For example, one of the original (now retracted) clinical trials demonstrating Lupron's effectiveness in the treatment of endometriosis was found to be based on data that was 80% fabricated by the principle investigator.⁴⁰ It has been alleged but not confirmed that other trials had similar fraudulent bases. Second, the manner in which Lupron is administered during an IVF protocol is quite different from the manner in which it is used to treat endometriosis or fibroids. When being treated for endometriosis or fibroids, women receive one injection of Lupron either every month or every three to six months. Conversely, women undergoing the most popular "long Lupron" protocol receive many days of consecutive injections, a regimen that is not at all reflective of the dosing for which the drug received its approval. Moreover, many women whose first IVF attempt ends in cancellation or

⁴⁰ Friedman, A. J., and M. D. Hornstein. "Gonadotropin-Releasing Hormone Agonist plus Estrogen-Progestin 'Add-Back' Therapy for Endometriosis-Related Pelvic Pain." *Fertility and Sterility* 60, no. 2 (August 1993): 236–41.

failure to conceive will undergo additional IVF cycles, and thus will undergo cyclical, sustained high doses of Lupron over the course of a few months. This also contradicts official recommendations which state that monthly injections of Lupron should be undertaken for a maximum of three months in the case of fibroids and six months in the case of endometriosis.⁴¹ For these reasons, Lupron's place in IVF remains hotly contested despite its approval for other women's health indications.

In addition to a general lack of data demonstrating Lupron's safety and efficacy in IVF (and perhaps women's health more generally), there is also a substantial body of evidence suggesting that the drug actually has long-term, irreversible negative effects on many women's physiology. It is now well established that, when used in the context of IVF, Lupron is associated with a significantly higher risk of the potentially life-threatening side effect of ovarian hyperstimulation syndrome (OHSS).⁴² OHSS can be brought on during IVF by the violent shift in a woman's hormones associated with the transition from the post-menopausal state induced by Lupron to a state wherein her ovaries are pharmaceutically triggered to produce as many eggs as possible. In other cases, Lupron has been linked to a directly opposing effect informally referred to by clinicians as "over-suppression." Over-suppression occurs when the hormonal suppression induced by Lupron is so powerful that egg production is halted even after the

⁴¹ U.S. Food and Drug Administration. LUPRON DEPOT® 3.75 mg Label. Reference ID: 3398735.

⁴² Golan, A., R. Ron-El, A. Herman, Z. Weinraub, Y. Soffer, and E. Caspi. "Ovarian Hyperstimulation Syndrome Following D-Trp-6 Luteinizing Hormone-Releasing Hormone Microcapsules and Menotropin for in Vitro Fertilization." *Fertility and Sterility* 50, no. 6 (December 1988): 912–16.

addition of hormonal stimulation.⁴³ Incidentally, both hyperstimulation and over-suppression result in a “failure” or “cancellation” of the IVF cycle that brought on the condition, making it necessary for the affected woman to start from the beginning if she intends to continue pursuing pregnancy via IVF.

In addition to these clinically well-documented side effects of Lupron in IVF protocols, there is a vast corpus of anecdotal reports from patients about permanently disabling side effects. These include such conditions as dramatic bone density loss (which the manufacturers of Lupron now admit is irreversible in some cases⁴⁴), thyroid dysfunction, joint deterioration, and cancer. There is a widely echoed claim within the post-IVF community that many fertility doctors, as well as the very labeling of the drug product itself, do not accurately present these side effects of Lupron to the patient. Indeed, even ostensibly impartial sources of information on Lupron contain shrouded suggestions about the severity of the potential harms of the drug. For instance, the WebMD page dedicated to Lupron features a peculiar and disconcerting reminder to patients in its side effects subsection: “*Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.*”⁴⁵ That such a reminder is deemed necessary is unsettling in itself. Equally unsettling is the

⁴³ “Over-suppression” has been extensively reported as a diagnosis given to women by their reproductive endocrinologists, though it has not been extensively studied.

⁴⁴ U.S. Food and Drug Administration. “NDA 019732/S-037 Lupron Depot 7.5 mg (leuprolide acetate for depot suspension).” Reference ID: 2888059

⁴⁵ “Lupron Subcutaneous : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing.” *WebMD*. Accessed October 2, 2015. <http://www.webmd.com/drugs/2/drug-6888/lupron-subq/details>.

language of the message, indicating that merely “many” (rather than “the majority of” or “most”) people who use Lupron do not experience severe side effects. The reader is led to wonder what has led to such a choice of words and whether there is some yet undisclosed evidence demonstrating that Lupron’s severe side effects are more common than they are portrayed to be. As these concerning and suspicious revelations about Lupron have escalated and yet continually fallen largely on deaf ears, the drug has gained notoriety as the alleged subject of a deliberate effort by manufacturers (and a willful negligence on the part of regulators) to downplay and hide its negative effects.

In recent years, former Lupron patients have begun to demand both resolution to the controversy and retribution for their suffering. Countless lawsuits have been filed against the makers of Lupron, both by individual plaintiffs as well as large class action suits, accusing the company of deliberately concealing its more severe associated health risks and bringing it to market on the basis of fallacious or insufficient evidence.⁴⁶ At least one of these lawsuits has reached the federal Ninth Circuit Court of Appeals.⁴⁷ Former Lupron patients have also begun to rally for legislative action, and as of October 4, 2015, a petition to the U.S. Congress requesting that the side effects of Lupron in women be investigated has received 8,807 signatures.⁴⁸ Patients whose health has been negatively affected by Lupron have also self-organized into several advocacy groups around the drug, the most prominent of which is the National Lupron Victims Network.

⁴⁶ Lupron | Dangerous Drug Information & Side Effects.” Accessed August 9, 2015. <http://www.adrugrecall.com/lupron/lupron.html>.

⁴⁷ Klein v. Abbott, et al. U.S. Court of Appeals for the Ninth Circuit. No. 11-17250.

⁴⁸ “Investigation into Lupron Side Effects (Leuprolide Acetate).” *Petition2Congress*. Accessed October 5, 2015. <http://www.petition2congress.com/1902/investigation-lupron-side-effects-leuprolide-acetate/>.

Patient groups have become increasingly active in pushing for their collective concerns to be addressed but have been thus far ineffective at generating any action from the drug's manufacturers or regulators.

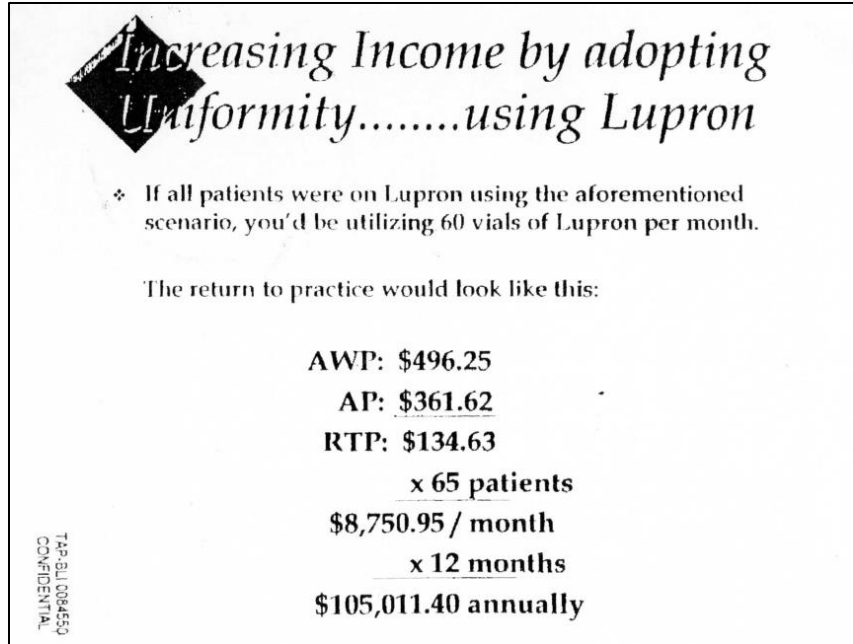


Fig 1: An internal TAP memo that was made public by the Oversight Hearings of the Commerce Committee as part of the investigation into the company's illegal marketing activities of Lupron. The memo outlines the income that would result from doctors prescribing Lupron to various numbers of patients.

An additional source of the contention about Lupron is the fact that it is not the most safe and effective drug of its class. Other GnRH agonists (mainly nafarelin and goserelin, or name-brand Synafel and Zoladex) have been found to be more effective than Lupron. However, even in the face of strong evidence that Lupron is less effective than these alternative pharmaceuticals, it has persisted for a remarkably long time as the near universal GnRH agonist of choice used in IVF protocols.⁴⁹ This may be partly the result of unlawful marketing strategies undertaken by its former manufacturer, TAP. In 2001, the U.S. Attorney brought charges against TAP for bribing doctors with medical equipment,

⁴⁹ Martin, Mary C., Carolyn R. Givens, Eldon D. Schriock, Robert H. Glass, and Pramila V. Dandekar. "The Choice of a Gonadotropin-Releasing Hormone Analog Influences Outcome of in Vitro Fertilization Treatment." *American Journal of Obstetrics and Gynecology* 170, no. 6 (June 1994): 1629–34. doi:10.1016/S0002-9378(94)70333-7.

grants, and vacations in exchange for prescribing Lupron as their principal GnRH agonist. Figure 1 represents one example of the profit-based advertising efforts that TAP undertook when marketing Lupron to medical practices. TAP paid \$875 million to settle these charges of health care fraud, which at the time was the largest health care fraud settlement in U.S. history.⁵⁰ In addition to providing illegal incentives, as early as 1997 TAP was providing doctors with promotional materials with false and disparaging information about their competitor drugs, an activity the company was cited for by the FDA on multiple occasions.⁵¹ Considering the previously cited estimated value of the market for Lupron, it is clear that a great deal of return is at stake in the domain of this drug. It is clear why its manufacturers would want to protect (and, to the greatest extent possible, even monopolize) the market for GnRH agonists.

Finally, IVF is not the only controversial off-label use of Lupron that has been documented. Lupron has been explored as treatment for an extraordinarily wide range of conditions, from Alzheimer's disease⁵² to atherosclerosis⁵³ to premenstrual syndrome.⁵⁴

⁵⁰ Petersen, Melody. "2 Drug Makers to Pay \$875 Million to Settle Fraud Case." *The New York Times*, October 4, 2001, sec. Business. <http://www.nytimes.com/2001/10/04/business/2-drug-makers-to-pay-875-million-to-settle-fraud-case.html>.

⁵¹ U.S. Department of Health & Human Services. Food and Drug Administration. Letter to TAP from the Division of Drug Marketing, Advertising and Communications. May 29, 1997.

⁵² Bowen, RL et al. "A clinical study of lupron depot in the treatment of women with Alzheimer's disease: preservation of cognitive function in patients taking an acetylcholinesterase inhibitor and treated with high dose lupron over 48 weeks." *Journal of Alzheimer's Disease* 44, no. 2 (2015): 549-560. doi: 10.3233/JAD-141626.

⁵³ Weisman, Kenneth M., and Michael Goldberg. Therapeutic uses of leuprolide acetate. US6099851 A, filed June 2, 1998, and issued August 8, 2000. <http://www.google.com/patents/US6099851>.

⁵⁴ Rubinow, David R., and Peter J. Schmidt. "Gonadal Steroid Regulation of Mood: The Lessons of Premenstrual Syndrome." *Frontiers in Neuroendocrinology* 27, no. 2 (July 2006): 210–16. doi:10.1016/j.yfrne.2006.02.003.

In addition, within recent years the hormonal suppression effects of the drug have generated interest in its potential as a method of chemical castration. A handful of physicians in the U.S. openly prescribe the drug to sex offenders and pedophiles (a largely male group) in order to “lower their testosterone, reduce their sex drive, and mitigate deviant desires.”⁵⁵ However, the objectionable dimensions of this use of Lupron are dissimilar to that of IVF in that they have little to do with the health and safety of the subject receiving the drug and more to do with violations of individual rights. Another even more controversial application of Lupron has been its use in the treatment of childhood autism. Championed by iconic anti-vaccination physician Mark Geier, the “Lupron protocol” for autism is widely considered by the scientific and medical community to be a case of unsubstantiated pseudoscience. Although Geier’s medical license was revoked in 2011, the Lupron protocol continues to receive attention as a legitimate treatment option, albeit to a far more limited extent,⁵⁶ and a patent application for use of Lupron to treat autism is still open and under review.⁵⁷ To a certain extent, the persistence of the debunked Lupron protocol for autism distantly echoes what is demonstrated by the case of Lupron’s role in IVF: that the subject of the “bad drug” narrative can endure, contrary to our expectations, in the face of significant discrediting

⁵⁵ Szalavitz, Maia. “Q&A: What Works in Sex-Offender Treatment.” *Time*. Accessed August 17, 2015. <http://healthland.time.com/2013/06/10/qa-what-works-in-sex-offender-treatment/>.

⁵⁶ Singer, Alison. “Complementary and Alternative Treatments for Autism Part 2: Identifying and Avoiding Non-Evidence-Based Treatments.” *AMA Journal of Ethics* 17, no. 4 (April 1, 2015): 375. doi:10.1001/journalofethics.2015.17.4.sect2-1504.

⁵⁷ Geier, Mark, and David Geier. Methods of treating autism and autism spectrum disorders. US20070254314 A1, filed October 30, 2006, and issued November 1, 2007. <http://www.google.com/patents/US20070254314>.

evidence. To explain how this can possibly be case requires us to disentangle and make sense of the various forces at work.

At a glance, the aforementioned account of Lupron might give this drug the outward appearance of being case of scandal, an outlier, and a bad drug that has slipped through the cracks. This is, however, not the case; for while Lupron may have indeed slipped through the cracks, it is not an outlier. What we regard as the cracks through which bad drugs slip in the context of the familiar narratives are actually built into the workings of the system. In a sense, all drugs slip through them. Thus, although Lupron does stand to defy our expectations through the degree to which it is entrenched in IVF, it only does so because our expectations are based on an incomplete understanding of drug normalization. If we buy into the bad drug narrative and all of its incompleteness, then the case of Lupron looks like a case of controversy. But if we set that narrative aside and look deeper then we can see that Lupron is controversial only on its face. In a much more fundamental way, it is not controversial at all and is in fact representative of the forces that are responsible for making all drugs. Lupron stands to help us expose, explain, and understand those forces, which will be the undertaking of subsequent sections.

SECTION III: THE TYPICAL SCENARIO

It is abundantly clear that Lupron's history mirrors the standard "bad drug" narrative in many ways. At the same time, it presents a challenge to this narrative in that no action has been taken to address the problematic dimensions of Lupron. Revelations about evidence of harm have been systematically unaddressed and Lupron continues to

be widely endorsed in its controversial applications. Such a bald defiance of our expectations leads us to ask: how this can possibly be? This simple but weighty question will be approached by first illustrating a typical scenario⁵⁸ of a woman who pursues infertility treatment in the form of an IVF protocol involving Lupron, then deconstructing that scenario to understand its contingencies. This seemingly ordinary, all too common scenario becomes quite extraordinary and worthy of interrogation when it is viewed with Lupron's rather abysmal track record in mind. We cannot help but ask what forces and factors must have converged in order to make it possible for this scenario to take place time and time again despite the it is contingent on the use of a classic "bad drug"?

* * *

A woman in her mid-thirties enters an infertility clinic. This is not her first appointment there. She and her husband have been trying to get pregnant for more than a year now with no success. After being evaluated at this clinic for possible causes of infertility, it was concluded that her fallopian tubes are blocked and she cannot become pregnant the "natural" way. She knows that IVF is her and her husband's last option that could allow them to have the child they have always wanted. By now, most of her friends have several children and she feels an increasing anxiety about her own inability to get pregnant, especially in light of her age. She's acutely aware that the time left on her biological clock is running down. And so, here she is at the clinic. She chose this

⁵⁸ The scenario is attempted composite of women's experiences in the pursuit infertility treatment and is based on stories that have been self-reported in forums, blogs, and other internet networking spaces.

particular infertility clinic because, after scouring the internet, she found that its advertised success rates for helping women get pregnant were quite high, although admittedly only slightly higher than other clinics. But of course she will opt for the best odds she can get, no matter how marginally better, especially when the treatment is so costly and not covered by her insurance.

At today's appointment she is consulting with her reproductive endocrinologist (RE), who has advised her that IVF is her best and probably only option for having a child. The RE reiterates the premise of IVF and then explains on a practical level how her cycle will work. First, he says, she will need to undergo several weeks of therapy on a variety of drugs in order to get her hormones in order. Her hormone production will initially need to be completely shut down in order to gain control over her reproductive system. This will be achieved with the drug leuprolide acetate, which she will administer to herself through a daily injection. This process of pharmaceutically shutting down her hormones, he notes, may come with certain side effects that are typically associated with menopause, such as hot flashes or some bone density loss. She may also experience mild bruising around the injection sites. Then, once her hormones have been shut off, her ovarian follicles will be stimulated with a different oral medication, clomiphene citrate, which will encourage her ovaries to produce and release eggs. Finally, she will receive one dose of a drug that will trigger all her eggs to mature, and two days later they will be harvested laparoscopically for fertilization and growth outside her body.

The woman is very excited about the prospect of truly beginning her medical journey to finally having a baby, but has a few reservations about the cost and the side

effects. The RE suggests that if the medications are too expensive then she might consider purchasing them online from an overseas vendor or buying other women's extra doses off Craigslist. This is, he says, common cost-cutting practice for women pursuing IVF on a budget. In response to her reservations about potential side effects of the drug therapy, the RE reassures her that although leuprolide acetate may cause some mild discomforts, this step of the process is extraordinarily important for the production of the maximum amount of high quality eggs. After all, the more high quality eggs, the more likely she is to end up with a baby. This reassurance is more than enough to put the woman's mind at ease. In any case, any pain and discomfort she might undergo is a worthy sacrifice in the pursuit of the ultimate goal: a baby of her own.

SECTION IV: UNRAVELING THE SCENARIO

The scenario illustrated in Section III is made possible by the convergence of countless social, cultural, political, economic, and regulatory elements. Of the various forces on which this scenario is contingent, three will be deconstructed and elaborated on in detail. Thus, Section IVF is divided into three parts:

1. The Ethical Tension behind Drug Regulation
2. (Bio)medicalization of Infertility: The Nature of the Beast
3. The Infertility Industry: Privatization, Competition, and Technocracy

It should be kept in mind that the types of relationships and factors described here are not unique to Lupron, IVF, and infertility, nor do they represent a comprehensive explanation

of the forces at play in the validation and proliferation of drugs and diseases more generally. Rather, these dimensions comprise an incomplete explanatory model of the contingencies that contribute to the popularization of individual drugs, both good and bad, in a society.

The Ethical Tension behind Drug Regulation

Perhaps the most significant source of tension associated with the application of Lupron in IVF is best captured by the words of Kathy Hudson, the Deputy Director for Science, Outreach and Policy at the National Institutes of Health. Responding to allegations that the safety and long-term effects of assisted reproductive technology (especially IVF) are questionable, Hudson commented:

“A number of practitioners and researchers in this field have said, Hey listen, you may say that we need more data, but meanwhile, people are longing for a healthy child. Their biological clocks are going off.”⁵⁹

Hudson’s candid breakdown of these circumstances illuminates an important reality: that oversight and regulation is an exercise in managing trade-offs. The most significant of these tradeoffs is between the potential benefit and potential harm of a given medical solution.

Before being introduced to the market, every drug is ostensibly tested with some amount of rigor to affirm its safety and efficacy. On one hand, collection of this evidence is intended to prevent potential maleficence that might be brought about by negative effects of the drug. On the other hand, the activities undertaken to collect this evidence

⁵⁹ “The Future of Research and Regulation for Infertility Treatments.” *Popular Science*. Accessed July 26, 2015. <http://www.popsoci.com/scitech/article/2003-02/future-research-and-regulation-infertility-treatments>.

inevitably delay (and in some cases, when the evidence thus indicates, permanently arrests) the processes of bringing a drug to market. The potential beneficence that might come from the use of a drug in question is therefore postponed by the processes that are designed to ensure its safety and efficacy. Regulatory bodies, namely the FDA, are tasked with determining how these two considerations, which are fundamentally at odds with one another, are to be balanced. Moreover, the FDA must not only determine *how much* evidence is needed but also *what quality* of evidence. In other words, when clinical trials of a drug demonstrate that it carries both positive benefits and negative side effects (as is often the case), the FDA must decide what severity and frequency of side effects is acceptable when considered in conjunction with the drug's desirable health effects. In this way, regulators must make decisions about how to balance both the temporal delay associated with evidence gathering as well as the negative findings of that evidence against the potential beneficence of a drug.

The standards established for achieving the risk-benefit balance in practice are manmade constructions. Stated so plainly, this point may seem obvious to us but is in fact a rarely-acknowledged dimension of regulatory standards. Regulatory standards are the product of ethical deliberations and value-laden decisions about how the aforementioned at-odds considerations—preventing harm and permitting benefit—ought to be weighed against one another. In this way, regulatory standards that may appear scientifically pristine on their face can actually be traced back to subjective value judgments. This reality often goes unrealized because these standards are invoked without any recognition of the values and processes that were used to establish them. In

this sense FDA regulatory standards represent something of a “black box” in the field of biomedicine. The box’s esteemed status and its capacity to churn out safe, effective medical solutions with some degree of reliability often lead us to take its inner workings and underlying assumptions for granted. However, in some cases—such as that of Lupron, as will be further discussed shortly—those workings and assumptions are more visible than others and allow us to glimpse the ethical tension at the core of regulation.

In addition to being the product of value judgments, the details of these regulatory standards are, in a certain way, arbitrary. For example, clinical trial data associated with a statistical p value of less than 0.05 is considered conclusively effective⁶⁰—but why was this figure established as the golden threshold? Why not a p value of less than 0.04, or less than 0.06? Why must clinical trials of drugs intended to treat chronic illnesses proceed for six months and not six-and-a-half or seven? Of course someone at some point in the past decided that this was to be the case. While those people may have been informed by experience, their decisions were ultimately an attempt to quantify previously discussed ethical tradeoff. Thus, even in cases when clear, firm ethical judgments can actually be made, packaging those decisions in the form of practical guidelines is at least somewhat of an arbitrary act.

Thus, the FDA’s regulatory standards are, upon close examination, quite pliable in nature. Nonetheless, these regulations are held up as and widely considered to be a rigorous gold standard for determining the safety and efficacy of a drug. Public trust in the quality and rigor of the FDA’s standards has consistently been and continues to be

⁶⁰ Katz, Russell. “FDA: Evidentiary Standards for Drug Development and Approval.” *NeuroRx* 1, no. 3 (July 2004): 307–16.

very strong.⁶¹ Recently, however, the pliable nature of these standards has been exposed rather unprecedented loosening of the commitment to the agency's traditional standards in certain cases. A well-known instance is the administration of the experimental drug ZMapp to a select few Ebola sufferers prior to the drug undergoing human trials.⁶² Another example is the passage of "right-to-try" bills in multiple states.⁶³ These pieces of legislation are designed with the intention of giving patients an opportunity to access investigational pharmaceuticals in cases where the patient's outlook is terminal and his or her life expectancy is low.⁶⁴ Both of these examples are characterized by a shift in the relative importance of the chief ethical considerations previously described. In these special cases, ensuring each drug's safety through evidence-based investigation was considered less important than allowing patients to access the potential benefits of the drug. The need of the patient is sufficiently urgent in these situations as to outweigh the potential harms of a drug that has not fully negotiated the traditional regulatory hurdles. Instances such as these wherein regulatory guidelines are circumstantially breached make evident that these standards are, at their core, rooted in value judgments.

⁶¹ Reinberg, S. "Americans Confused About FDA and Drug Safety." *ABC News*, March 24, 2008. <http://abcnews.go.com/Health/Healthday/story?id=4508750&page=1> and Slater, Eve E. "Today's FDA." *New England Journal of Medicine* 352, no. 3 (January 20, 2005): 293–97. doi:10.1056/NEJMs042278.

⁶² Associated Press. "Experimental Ebola Drug: Questions and Answers about ZMapp." Accessed September 2, 2015. <http://www.cbsnews.com/news/experimental-ebola-drug-questions-and-answers-about-zmapp/>.

⁶³ Zettler PJ, and Greely HT. "The Strange Allure of State 'right-to-Try' Laws." *JAMA Internal Medicine* 174, no. 12 (December 1, 2014): 1885–86. doi:10.1001/jamainternmed.2014.5767.

⁶⁴ The ability of right-to-try laws to have a real impact on patients' access to investigational pharmaceuticals is debatable. This is because, under these laws, drug manufacturers have the right to refuse to provide their investigational products. Even in cases where companies are compliant they have the right to charge for these products, which are not covered by insurance. Barriers such as these call into question the practical effectiveness of right-to-try legislation.

At this point in our discussion of tradeoffs and value judgments in pharmacy, it is appropriate to recall the reminder found on the Wed MD page for Lupron (“*Remember that your doctor has prescribed this medication because he or she has judged that **the benefit to you is greater than the risk of side effects***”) as an unusually explicit acknowledgment of the ethical balancing act underpinning its use. Indeed, like the previously described cases, the use of Lupron in IVF is a case that illuminates the interplay of harm and benefit that underlies the approval and use of all drugs. But what is it about the case of Lupron that makes visible these constitutive ethical tradeoffs and value judgments? First, Lupron has something noteworthy in common with drugs that have been permitted to sidestep the FDA’s honored standards in the name of beneficence; that is, IVF (and, by extension, Lupron) seeks to address an ostensive problem—female infertility—that is of an urgent and time-sensitive nature. It is true that Lupron has not met—and perhaps, with further testing, would fail to meet—the FDA’s regulatory standards for use in IVF. But, as Kathy Hudson points out in no unclear terms, calls for further testing and a higher standard of evidence have been largely drowned out by the ticking of women’s biological clocks telling them that, like terminal cancer patients or Ebola victims, their window of time to take advantage of Lupron and IVF is small and constantly shrinking.

However, although the temporal dimension of infertility may be similar to conditions like terminal cancer or Ebola, it differs from these cases in a glaring way. That is, female infertility is not at all life-threatening, nor is it even life-shortening. In fact, infertility is only harmful insofar as the inability to produce children is harmful. The

manifestations of this harm are not strictly physical, but rather mental, emotional, and perhaps psychosomatic. Hence, whereas in other cases a lower standard of evidence and assumption of greater risk might be considered ethically acceptable due to the threat of impending death, the risks associated with Lupron as used in IVF simply cannot be justified under this logic. Instead, what is at stake in cases of infertility is the psychological harm associated with the failure to fulfill implicit and explicit expectations of parenthood. Thus, although today infertility is widely considered to be a medical problem, at its most elementary level it is a sociocultural problem. The landscape of infertility is therefore charged with values that inevitably play into the basic risk-benefit tradeoff underlying treatments that seek to address it.

A final note on the topic of evidence, risk, benefit, and regulation is that the complex protocols used in IVF today were performed successfully in humans before even being attempted in higher animal models. The first baby conceived via IVF was born in 1979, but it wasn't until 1987 that IVF testing began in baboons, with chimpanzees following even later.⁶⁵ Many of the techniques used in later-generation IVF have never been tested in animals. This breach of the standard procedures for evaluating safety and efficacy is another example of how ethical tradeoffs, although not always visible, are at the core of the operations of biomedicine. Bypassing animal testing and moving straight to human experimentation undoubtedly allows this technology to enter the public sphere more expediently than if the official tiered testing of animal models had been followed. Undoubtedly a larger number of infertile people to date have been able to have children

⁶⁵ Groenhout, Ruth E. *Connected Lives: Human Nature and an Ethics of Care*. Rowman & Littlefield, 2004.

because of this, and so skipping animal testing arguably provided some amount of value-laden benefit. However, another force at play which is not a matter of ethics is profit motive, which also incentivizes a less thorough testing process. At what cost these compromises have been made remains to be seen.

(Bio)medicalization of Infertility: the Nature of the Beast

I have just completed a discussion of the way in which decisions about drug regulation are rooted in an ethical tension between the potential harm and potential benefit of a drug. As discussed in the previous section, one point of discretion in determining how a drug might be used toward solving particular medical problem lies in the question of “how grave is this problem?” Therefore, decisions about the magnitude of a drug’s potential benefit are critically linked to the conceptualization of the condition the drug is aiming to treat, i.e., what problem it is aiming to solve. However, another point of discretion is buried in the question of “why do we consider this a (medical) problem?” As is true of the establishment of regulatory standards, someone at some point—or, more accurately, many people over a period of time—decided that the condition of interest represented a problematic state, and a medical one at that. In the case of Lupron and IVF, it is important to take a closer look at its target condition, infertility, and the way that it has come to be construed as a medical problem—or, the biomedicalization of infertility.

Biomedicalization is the next generation of medicalization. Medicalization theory describes the processes by which human statuses come to be construed as medical problems and the general expansion of medicine into broader and deeper arenas of human

life. The early champions of medicalization described it as a movement from “badness to sickness,” or in other words a trend toward reinvention of social problems in medical terms.⁶⁶ Thus, medicalization revealed the reality that medicine has a sociocultural dimension and the designation of disease states relies on implicit and explicit sociocultural values. Although such a reality remains true today, medicalization is now inadequate to account for the degree of complexity and novel set of dynamics that have come to dominate medicine in recent decades. Thus, the biomedicalization framework was proposed to build upon medicalization and make sense of these new developments.

Biomedicalization describes the body of processes at work in post-modern medicine that contribute not only to the shift of human statuses and conditions into the purview of medicine but also the sociocultural, economic, institutional forces that are co-constitutive of the remaking of medicine today. For example, the framework describes such developments as the increasing corporatization of medicine, the commodification of health, and a heightened emphasis on self-surveillance of health risks.⁶⁷ These and other processes described by biomedicalization are quite relevant to the case of medical infertility and its treatments. Although infertility was initially the product of medicalization, it has subsequently been (and continues to be) reshaped by the forces of biomedicalization. For example, while medicalization describes a regime wherein doctors are the gatekeepers of medicine for their patient populations, biomedicalization

⁶⁶ Conrad, Peter, and Joseph W. Schneider. *Deviance and Medicalization: From Badness to Sickness*. Philadelphia: Temple University Press, 1992.

⁶⁷ Clarke, Adele E. et al., eds. *Biomedicalization: Technoscience, Health, and Illness in the U.S.* 1 edition. Durham, NC: Duke University Press Books, 2010. Print.

points to the fact that patients are now gathering knowledge in new, varied, and stratified ways. We can see these realities play out in IVF insofar as infertility patients take the knowledge production and consumption process surrounding their treatment into their own hands. As patients seek advice and gather expertise from diverse sources (ranging from scholarly journal articles to other women's anecdotal experiences) they not only consume but also contribute to the production of popular knowledge on these topics. All of these exchanges are deeply facilitated by internet media. Thus, doctors no longer represent the sole (or even primary) source of medical expertise. In addition, while medicalization describes doctor and patient roles that are based on more traditional configurations of providing public good, biomedicalization depicts a state of medicine wherein patients act as consumers and doctors act as vendors of products and services. Thus, in the era of biomedicalization, doctors and patients are burdened with a different and more complex set of rights and responsibilities as compared to the era of medicalization, when patient care was less entwined in market enterprise. This configuration is precisely reflected in the roles taken on by the doctors and patients of the infertility industry, as will be discussed more thoroughly in the next subsection. It is for these reasons, among others, that biomedicalization is a useful framework to adapt to the case of infertility and make sense of its present state of entanglement in medicine.

Rather than provide a more complete historical account of the processes by which infertility has come to be thought of as a medical problem, I will instead provide a brief explanation of the values and structures that support this categorization, followed by a more detailed account of the effects and outcomes of the biomedicalization of infertility.

Tracking these outcomes has important consequences for understanding the current state of the infertility industry and its roots in broader trends in biomedicine.

* * *

At the most basic level, designation of a human status or condition as medically problematic—i.e., a disease—is founded in the basic principle that pain and suffering are undesirable and should be avoided and/or resolved. However, what counts as pain and suffering is mediated by certain sociocultural contingencies. The role that sociocultural construction plays in a disease designation varies in its visibility from case to case. To offer a rather extreme juxtaposition of examples, while Ebola seems straightforwardly problematic in that causes intense physical suffering and often death, ADHD is considered problematic for in that it decreases the ability to be productive and successful by whatever definitions of productivity and success prevail in society. Clearly, socioculturally constructed values are more readily apparent in the latter of these two examples as a defined disease state. In all cases it is worthwhile to examine those values on which the disease is founded and assess the weight that they carry in answering the question of “why do we consider this a (medical) problem?” As it so happens, in the case of Lupron these values are quite baldly visible and thus the story is easy to read in these terms.

The single most important value at play in the treatment of infertility in the U.S. is that of pronatalism, or the importance of having biological children. This value is not

only active in the risk-benefit assessments made by systems and individuals about solutions to infertility, but is actually co-constitutive of the very medical conceptualization of infertility. As previously stated, today in the U.S. the inability to bear children is firmly considered to reside firmly within the purview of medicine, but this categorization is a relatively recent historical development.⁶⁸ The fact that doctors today are able to diagnosis of such a thing as “infertility” is the result of the gradual medicalization of a fundamentally social condition formerly referred to as “involuntary childlessness.” In order to understand the critical role that values such as pronatalism, reproductive autonomy, and others continue to retain in medicalized infertility, an account of the sociocultural basis of infertility is warranted.

As a disease state, infertility is rooted in concepts of deviancy versus normalcy. In essence, women who are unable to conceive and/or give birth are assigned a status that is “deviant” because it violates sociocultural expectations of childbearing. Such pronatalistic expectations and the importance of childbearing are deeply entrenched in American society.⁶⁹ These values have been so pervasive that, for many years, medical documentation of infertility was even required in order to submit an infant adoption application.⁷⁰ Today, studies show that contemporary Americans continue to think of childbearing and parenthood as paramount for a number of reasons. The most prominent

⁶⁸ “WGBH American Experience | PBS.” *American Experience*. Accessed September 15, 2015. <http://www.pbs.org/wgbh/americanexperience/features/timeline/babies/>.

⁶⁹ It has been argued by sociologist Arthur Greil that the paramount importance of children in American society can be partly explained by American individualism, leading to a pervasive “lack...of moral purpose beyond the level of individual experience and interpersonal relationships.”

⁷⁰ Miall, Charlene E. “The Stigma of Involuntary Childlessness.” *Social Problems* 33, no. 4 (April 1, 1986): 268–82. doi:10.2307/800719.

of these include children's capacity to provide love, stimulation, a kind of immortality,⁷¹ a sense of accomplishment, and, most importantly for the purposes of this discussion, a sense of *adulthood* and *social identity*. These last two factors are critically important for understanding the manner in which sociocultural expectations underpin the act of having children. American adults report that having children is the single most important life event that leads them to feel that they have achieved competent adulthood and that they have "grown up" in the eyes of society.⁷² Thus, biological children undoubtedly represent a critical component of the culturally-constructed model American adult.

The model American adult, however, is a gendered construction. For women, childbearing plays a more central and sweeping role in defining sociocultural identity as compared to men,⁷³ a status that has been historically perpetuated by cultural and religious lore throughout the world.⁷⁴ Therefore, despite the fact that the underlying causes of infertility can be attributed to both men and women at equal rates, the responsibility for and emotional consequences of infertility are not equally distributed. As a result women who are unable to bear children are more heavily stigmatized than

⁷¹ Studies show that many parents consider children valuable as a way to cope with the ephemeral nature of life. Parents view children as an extension of themselves both in terms of biological ties and personal values. In this way, children expand their parents' sense of personal significance by linking them to the past and future indefinite.

⁷² Hoffman, Lois Wladis, and Jean Denby Manis. "The Value of Children in the United States: A New Approach to the Study of Fertility." *Journal of Marriage and Family* 41, no. 3 (August 1, 1979): 583–96. doi:10.2307/351628.

⁷³ Cousineau, Tara M., and Alice D. Domar. "Psychological Impact of Infertility." *Best Practice & Research Clinical Obstetrics & Gynaecology*, Psychological Issues in Obstetrics and Gynaecology, 21, no. 2 (April 2007): 293–308. doi:10.1016/j.bpobgyn.2006.12.003.

⁷⁴ Greil, Arthur L. *Not yet Pregnant: Infertile Couples in Contemporary America*. New Brunswick [N.J.]: Rutgers University Press, 1991.

men in the same position and report that infertility is a greater relative blow to their personal identity and social standing. Women often believe that infertility prevents them from achieving womanhood and fulfilling a role in their life that is critical to their sense of self.⁷⁵ In fact, fertility and childbearing are such a significant element of the female sociocultural function that women often keep secret the fact that they are pursuing fertility treatment so as not to expose their condition and the shame associated with it.⁷⁶

It is without a doubt that the pressure of pronatalistic societal values has long fallen unevenly on the shoulders of women, and thus the harm of infertility is especially relevant for them insofar as it manifests in social stigmatization, isolation, identity crisis, and psychological distress. The reallocation of childbearing problems to the medical field over the course of the 20th century has done little to change this but rather, according to Becker and Nachtigall, has simply served as a way of “managing difference from the norm.”⁷⁷ In other words, medicalization of the inability to bear children has offered a way to negotiate the element of social deviancy attached to this condition. For instance, the emergence of infertility as a diagnosis has assigned a sense of evidential legitimacy (whether justified or not) to those affected by it by relegating the source of their suffering to the biomedical sciences. However, even so, the legitimacy of infertility as a medical

⁷⁵ Cousineau, Tara M., and Alice D. Domar. “Psychological Impact of Infertility.” *Best Practice & Research Clinical Obstetrics & Gynaecology*, Psychological Issues in Obstetrics and Gynaecology, 21, no. 2 (April 2007): 293–308. doi:10.1016/j.bpobgyn.2006.12.003.

⁷⁶ Becker, Gay, and Robert D. Nachtigall. “Eager for Medicalisation: The Social Production of Infertility as a Disease.” *Sociology of Health & Illness* 14, no. 4 (December 1, 1992): 456–71. doi:10.1111/1467-9566.ep10493093.

⁷⁷ Becker, Gay, and Robert D. Nachtigall. “Eager for Medicalisation: The Social Production of Infertility as a Disease.” *Sociology of Health & Illness* 14, no. 4 (December 1, 1992): 456–71. doi:10.1111/1467-9566.ep10493093.

condition today remains largely contingent on the persistence of pronatalistic sociocultural values.

Although the consignment of childbearing problems to medicine has in no way altered the pronatalistic foundations of infertility, it has had a variety of other effects. As infertility came to be medicalized and later biomedicalized, the range of decisions that individuals and couples are able to make about how to approach the problem has seemingly been expanded. Assisted reproductive technologies and pharmaceutical solutions have emerged and become widely normalized. Thus, a cursory glance at the field would lead to the conclusion that women's reproductive rights have been reaffirmed with the availability of these new medical choices. However, in a different sense the relegation of infertility to healthcare has also constricted women's choices in several ways. These constrictions have created a set of conditions that has allowed IVF and Lupron to flourish even in spite of the latter's notoriety. It should be kept in mind that the impacts of the biomedicalization of infertility described hereafter are also relevant to the way in which other diseases are affected as they become ensconced in the operations of post-modern medicine.

The first way in which biomedicalization has altered the landscape of infertility is through the provision of biotechnological solutions (most notably IVF) that allow babies to be made under previously impossible circumstances. The availability of these solutions has caused neglect of other options for infertile couples such as adoption or acceptance of a childless lifestyle. Notably, the acceptability and popularity of these options had been on the rise since the 1970s as a result of the emergence of the feminist

movement, which contributed much to the expansion of women's sociocultural roles from their previously narrow childbearing domain and began to temper the prevalence of gendered pronatalistic values. However, more recently some of this progress has been backpedaled as the popularization of assisted reproductive technologies such as IVF has generated what has been referred to as a "resurgence of pronatalist sentiment" and a renewed emphasis on the importance of biological children.⁷⁸ Thus, medicalization has reaffirmed ideals that encourage women to try to overcome their infertility rather than accepting it or taking other courses.

Secondly, the women and couples who choose to try to overcome their infertility are invited to take a medical approach to tackling this ostensive problem and this, too, places restrictions on their choices. The fact that Western medicine is increasingly becoming the primary acceptable manner by which to confront infertility can be linked to a broader trend whereby medicine has pervaded human life with increasing broadness and depth. Meanwhile, it is not clear that the Western medicine approach is particularly exceptional at the goal of producing babies. One longitudinal study of infertile couples who did and did not seek medical treatment found that "while 41 percent of couples treated for infertility subsequently conceived, so did 35 percent of those who had not received treatment."⁷⁹ If generalizable, these findings indicate that medical treatment only marginally improves the odds of overcoming infertility. In addition, the high

⁷⁸ Donchin, Anne. "Feminist Critiques of New Fertility Technologies: Implications for Social Policy." *Journal of Medicine and Philosophy* 21, no. 5 (October 1, 1996): 475–98. doi:10.1093/jmp/21.5.475.

⁷⁹ Greil, Arthur L. *Not yet Pregnant: Infertile Couples in Contemporary America*. New Brunswick [N.J.]: Rutgers University Press, 1991.

success of non-Western methods for overcoming infertility suggests that Western medicine cannot be justified as the clearly superior approach. For example, anthropologists have found that traditional Kenyan healers have a 33% success rate at resolving infertility problems.⁸⁰ In addition, traditional Chinese herbal medicine has been found to be even more effective than Western biomedical approaches with a 60% success rate.⁸¹ And yet, in the U.S. these alternative approaches are almost completely overlooked in favor of biomedical technologies. Moreover, although the number of women in the U.S. who seek treatment for infertility overall is decreasing annually, the number of women who undergoing IVF continues to rise. Thus, the availability of IVF may be further constricting women's choices by steering them toward the highest-tech (and, incidentally, also most expensive) medical option.⁸²

The confinement of women's choices about how to approach infertility to the scope of medicine also encourages them to evaluate those choices in a particular way. As discussed in the previous sub-section, there is a distinctive logic used in the process of assessing risk-benefit tradeoffs in the context Western medicine. This logic, although perhaps presented as objective, is in fact pervaded by gendered sociocultural values including the importance of reproductive rights and especially pronatalism. The latent grip of these values often manifests in women's medical decisions with regard to treating

⁸⁰ Katz, Sydney S., and Selig H. Katz. "An Evaluation of Traditional Therapy for Barrenness." *Medical Anthropology Quarterly* 1, no. 4 (December 1, 1987): 394–405. doi:10.1525/maq.1987.1.4.02a00030.

⁸¹ Ried, Karin, and Keren Stuart. "Efficacy of Traditional Chinese Herbal Medicine in the Management of Female Infertility: A Systematic Review." *Complementary Therapies in Medicine* 19, no. 6 (December 2011): 319–31. doi:10.1016/j.ctim.2011.09.003.

⁸² Gholipour, Bahar. "Fewer Women Seeking Help for Infertility." *LiveScience.com*. Accessed September 25, 2015. <http://www.livescience.com/42750-fewer-women-seeking-help-infertility.html>.

their infertility. Becker and Nachtigall have reported on the way that risk assessment is undertaken in the context of American medicine and how it can lead women to take on greater risks as they pursue pregnancy through medical treatment. Their conclusions neatly describe the nature of this phenomenon:

“[Our] research suggests that once infertility is medically designated as a disease, both patients and practitioners pursue a ‘cure’ through a well-delineated pattern of medical treatment, despite the risks of such treatment and independent of the likelihood of success. *When medical views of risk and responsibility are teamed with women’s persistence in the pursuit of a pregnancy, medical treatment may be taken to extremes.* Americans consider risk-taking to be their prerogative when personal histories reflect strong cultural mandates about norms, values, rights, and responsibilities, and these in turn are interpreted as health-related by both consumers and health professionals.”⁸³ [emphasis added]

Thus, medicalized infertility is a space where the American cultural constructions of risk comes face to face with entrenched, gendered pronatalistic values, and these forces together can lead to systemic patterns of hazardous health decisions on the part of women pursuing treatment. All signs point to women taking the iconic duo of “safety and efficacy” and throwing the former to the wind in the name of the latter.

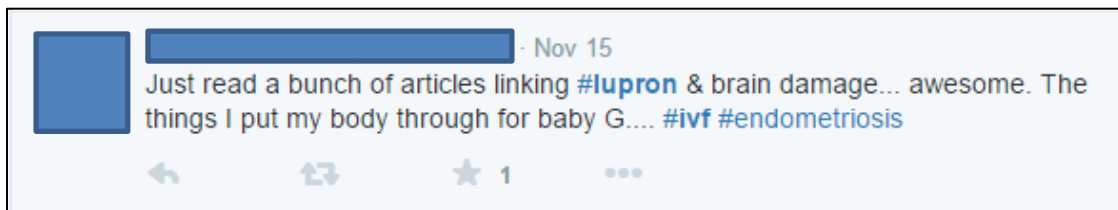


Fig 2: A tweet from a woman who was, at the time, undergoing an IVF protocol involving Lupron exemplifies the type of risk rationalization that is characteristic of women in this position.

⁸³ Becker, Gay, and Robert D. Nachtigall. “‘Born to Be a Mother’: The Cultural Construction of Risk in Infertility Treatment in the U.S.” *Social Science & Medicine* 39, no. 4 (August 1994): 507. doi:doi:10.1016/0277-9536(94)90093-0.

This configuration is certainly at play more specifically in the way that women engage with the drug Lupron. Figure 2 displays one woman's tweet concerning her use of Lupron as she pursues infertility treatment through IVF. At the time of this posting, this woman had been undergoing infertility treatment with no success for a duration of nearly two years. Based on her circumstances and the language she uses in this tweet, it is clear that she is tenacious in her willingness to shoulder enormous risks and make personal health sacrifices (including gambling with the possibility of brain damage⁸⁴) all for the sake of "baby G," who has not even been conceived. The message she expresses exemplifies the patterns of risk rationalization exhibited by women and couples who are faced with medical decisions about their infertile condition and must assess the potential harms and benefits of their options.

This message is similarly evoked by Figure 3, a viral Facebook photo that was shared to the page of an infertility clinic by one of its customers who successfully conceived and subsequently gave birth to the pictured baby. The surrounding heart is constructed from a fraction of the discarded syringes that were used in the process of the mother's infertility treatment. The mother underwent five IVF cycles before her successful pregnancy was achieved.⁸⁵ The darkly cheerful figure and its caption evokes the way in which cultural construction of risk in the U.S. leads women to undertake the

⁸⁴ In a number of cases, Lupron has been found to cause irreversible dementia, memory impairment, and pituitary apoplexy. Only the last of these three types of brain dysfunctions is reported as a side effect on the current label for Lupron, despite being less frequently reported than the previous two.

⁸⁵ "Why Is This Baby Surrounded by Syringes?" *TODAY.com*, October 9, 2015. <http://www.today.com/parents/moms-photo-ivf-baby-surrounded-syringes-inspires-potential-parents-t49276>.



Fig 3: a viral Facebook photo shows a woman’s newborn, conceived via IVF, surrounded by some of the used syringes of the fertility drugs (including Lupron) that were used to conceive her. The caption reads: “Thank you to Sher Fertility St. Louis and Dr. Dayal patient Angela, who shows the true definition of love that went into making this gorgeous new baby

risk and pain associated with IVF as part of their personal mission and perceive the intensity of that risk to be a reflection of their resolve in the pursuit of motherhood.

A final function that has been carried out by the medicalization of infertility lies in the reality that modern medicine is an industry. By taking the involuntary lack of children from a social problem (which doesn’t provide opportunities for solutions) to a medical problem, the status of infertility gains an economic dimension. A new space in the pharmaceutical, medical, biotechnological market is opened and invites itself to be filled with solutions. The transition from sociocultural deviant to medical patient also represents an unavoidable transition from sociocultural deviant to consumer. Therefore the relegation of infertility to the realm of medicine amounts to commodification of childbearing and babies. This is because post-modern medicine is an industry that is subject to market logic. Biomedicalizing infertility has turned offspring into a

commodity that can be bought and sold.⁸⁶ The importance of this dimension will be expanded upon in more depth throughout the subsequent section.

The Infertility Industry: Privatization, Competition, and Technocracy

In recent decades, medicine has been transformed into an ever more industrialized and commercialized enterprise. In this enterprise, health and its derivatives have become commodities, the line between providing care and conducting business has been blurred, and the patient has been made to assume the additional role of consumer.⁸⁷ These dramatic changes to the face of medicine have a profound effect on the mechanisms by which drugs are normalized. Thus, it is important to examine the market space in which both producers and consumers are operating and the politico-economic circumstances that guide these actors' discretion as they navigate the market. Of course these circumstances vary from drug to drug. In particular, the case of Lupron and the infertility industry is characterized by a dizzying confluence of politico-economic circumstances (including privatization, competition, lack of regulation, and others) that make it an ideal exemplar to illuminate an array of factors that may play a role in the normalization of drugs more generally.

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⁸⁶ Spar, Debora L. *The Baby Business: How Money, Science, and Politics Drive the Commerce of Conception*. 1 edition. Boston: Harvard Business Review Press, 2006.

⁸⁷ Clarke, Adele E. et al., eds. *Biomedicalization: Technoscience, Health, and Illness in the U.S.* 1 edition. Durham, NC: Duke University Press Books, 2010. Print.

Like many sectors of medicine in the U.S., the treatment of infertility is not so much of a field as it is a medical-industrial complex. It is dominated by private institutions and technocratic formulations of authority, and has been widely referred to as the “wild west” of the medical world.⁸⁸ While this extreme characterization might be arguable, there is no doubt that the American infertility industry is uniquely unwelcoming to regulation and governance. This attribute of the infertility industry makes perfect sense, however, when viewed through a historical lens. Indeed, separation from the establishment was a quality of the industry’s configuration almost from the very moment it emerged. Notably, although today this separation is perpetuated by the actors in the industry (who have come to quite like the landscape of the “wild west” and the advantages it offers them), it was first brought about as a result of actions on the part of the healthcare governance bodies.⁸⁹ During the formative years of medicalized infertility and IVF, the U.S. (and to perhaps a lesser extent, the U.K.) was quite hostile to the notion of test tube babies and assumed a stance of resounding opposition to research in this arena. Researchers who ignored this opposition and continued to perform work in this area were cast out of mainstream institutions. Although the pioneers of IVF sought funding from and use of government institutions they were denied on the basis that their work was morally indefensible, resulting in such debacles as the botched Del Zio IVF

⁸⁸ Spar, Deborah L. “Making Laws About Making Babies: Fertility Industry Is a Wild West.” *The New York Times*. Accessed October 14, 2015. <http://www.nytimes.com/roomfordebate/2011/09/13/making-laws-about-making-babies/fertility-industry-is-a-wild-west>.

⁸⁹ Lahl, Jennifer. “The Resistance: Sex, Lies and Greed.” *The Center for Bioethics and Culture*. Accessed October 15, 2015. <http://www.cbc-network.org/2010/04/the-resistance-sex-lies-and-greed/>.

attempt.⁹⁰ Even after the successful birth of Louise Brown, Edwards and Steptoe hoped to continue their work under the NHS, but were rejected on ethical grounds. Instead, they were forced to found a private infertility clinic, as were many physicians and researchers in the U.S. who wished to continue work in this field.⁹¹ Thus has emerged an industry that was forged outside of the bounds of mainstream medical institutions and has as a result developed into deeply privatized, commercialized, and technocratic domain.

Today, the infertility industry has a strange relationship with the establishment that rejected it for so long. IVF and other assisted reproductive technologies have become far more accepted and at this point are quite normalized in society and rarely contested on moral grounds. The shift in the ethical permissibility of IVF technology is also reflected in the fact that it is longer the case that mainstream medical institutions want nothing to do with the field. In fact, the 2010 Nobel Prize in medicine was awarded to Robert Edwards, one of the researchers responsible for the world's first IVF baby, for his years of work dedicated to refining the technique.⁹² However, it is now the case that the infertility industry has become an establishment in its own right and consistently resists attempts of governance bodies to establish standards, guidelines, policies, and other regulatory rules for the industry. IVF procedures at some fertility clinics undergo IRB review, but only if these clinics are associated with institutions that receive some

⁹⁰ “WGBH American Experience . Test Tube Babies | PBS.” *American Experience*. Accessed September 20, 2015. <http://www.pbs.org/wgbh/americanexperience/features/timeline/babies/>.

⁹¹ Brian, Kate. “The Amazing Story of IVF: 35 Years and Five Million Babies Later.” *The Guardian*, July 12, 2013, sec. Society. <http://www.theguardian.com/society/2013/jul/12/story-ivf-five-million-babies>.

⁹² The Nobel Assembly at Karolinsky Institutet. “PRESS RELEASE 2010-10-04 The Nobel Assembly at Karolinska Institutet Has Today Decided to Award The Nobel Prize in Physiology or Medicine 2010 to Robert G. Edwards for the Development of in Vitro Fertilization,” October 4, 2010.

form of federal funding. The great majority of clinics are private and therefore carry out procedures and techniques that have not been subject to evaluation of their safety, efficacy, or ethicalness by a public oversight body outside of the industry. Rather, the American Society for Reproductive Medicine—the industry’s foremost authority body—has established its own accreditation program for clinics as well as training and certification for practitioners in the field. Even more subtly, however, the industry space is pervaded by implicit set of uncodified norms that define way that infertility medicine is practiced and the dynamics between actors play out. This self-moderated regime has resulted in a great deal of methodological freedom for infertility doctors, the clinics they work for, and the pharmaceutical and biotech companies that supply their needs. The industry’s freedom and hands-off attitude toward third-party oversight is such that potential harms of its medical practices may go unnoticed or unacknowledged, even when those practices are routine and well-accepted.

Infertility specialists are not the only group that may benefit from the “wild west” regime of their industry. Many patients, too, take the free operations of the industry to be a natural and expected affirmation of their reproductive autonomy. Adele Clarke and her colleagues describe the nature of the industry aptly, remarking that “Ideals of ownership and individualism punctuate reproductive practices and services as reproduction becomes another do-it-yourself project enabling us to transform our selves, identities, and social lives through consumption.”⁹³ Women and couples seeking infertility treatment value the

⁹³ Clarke, Adele E., Laura Mamo, Jennifer Ruth Fosket, Jennifer R. Fishman, and Janet K. Shim, eds. *Biomedicalization: Technoscience, Health, and Illness in the U.S.* 1 edition. Durham, NC: Duke University Press Books, 2010.

ability to pursue different options and customize their treatment, even in ways that are ethically controversial. Regulation from outside of the industry would limit the range ways that their treatment could play out in practice. For example, pieces of legislature have been proposed that would limit the number of eggs that can be implanted into a woman or make financial compensation for egg donation illegal. However, these proposals have been violently contested by physicians who operate in the industry as well as its consumers. Jennifer Lahl, the national director for the Center for Bioethics and Culture captured the vehemence of this position in recollecting her experience in one legislative effort: “I recall testifying to the Georgia State Senate in 2009...what really caught me off guard were the throngs of women who held pictures of their IVF babies, accusing me of trying to steal their reproductive rights.” It is abundantly clear that notions of reproductive rights and autonomy play an important role in perpetuating a certain regime of self-maintained norms within the infertility industry. The notion of consumer protections is not acknowledged in this space where the dominant paradigm is that of consumers’ reproductive rights (including the right to not be protected and to undertake risks).

At this point it is necessary to address and justify the use of the term “consumer” in this context; for although the medicalization of infertility has certainly led women to assume the role of “patient,” the economic configuration of the reproductive medicine (and indeed the industrial nature of post-modern medicine at large) has also led them to take on the role of “consumer.” This is a characterization makes many people uncomfortable because it amounts to assigning a price to human life, reducing its production to a series of transactions, and acknowledges the dimension of profit attached to such transactions. But however uncomfortable, there is undoubtedly a certain truth evoked by labeling the patrons of the infertility industry as consumers. On the one hand, the fact that patrons of the infertility industry are acting as consumers is quite obvious and not surprising. However, there are important implications attached to a system wherein patients are cast as consumers and healthcare practitioners are cast as producers and vendors of goods and services. In particular, the consumer-producer configuration reflects on the responsibilities and behaviors of different actors and the dynamics that exist between them. For example, compared to a more traditional doctor-patient configuration of healthcare, the clients of the infertility industry are responsible for their choices and are positioned to “shop



Fig 4: A controversial advertisement for a contest hosted by a Canadian radio station that awarded an infertile couple with payment for their IVF treatment.

around” for the product/service that suits them best. Patrons are not only seeking the most suitable treatment in a personal sense but also in a financial sense, and thus are executing cost-benefit tradeoff logic—market logic—in a quite literal manner. This arrangement, wherein the healthcare subject is the primary negotiator of decisions who interfaces directly with the businesses that provide them, has both produced and been the effect of a regime in which the reproductive rights of consumers are considered more important than consumer protections. The infertility clinic, on the other hand, is responsible for providing products and services that will meet clients’ expectations (in this case, the expectation of having a baby) while at the same time profiting from the transaction. The obligations of infertility clinicians, therefore, are comprised of a variety of considerations that complicate physicians’ more traditional commitment to providing a public good; for in addition to operating as medical doctors providing a public good, they are also operating as businesspeople providing a commodity.

Indeed, today more than ever, babies are a commodity that can be bought and sold. The treatment of infertility through medicine and technology has turned babies into a product that results from the convergence of goods and services of various market segments, from the pharmaceutical and biotechnological sectors to human services like donation and surrogacy.⁹⁴ Sometimes the commodified state of babies and childbearing is entirely explicit, such as in the advertisement given in Figure 2 wherein a human infant

⁹⁴ Spar, Debora L. *The Baby Business: How Money, Science, and Politics Drive the Commerce of Conception*. 1 edition. Boston: Harvard Business Review Press, 2006.

was held up as the prize for a Canadian radio contest.⁹⁵ Of course the human infant featured in the ad was not the prize in itself, but instead the station was offering to pay for one “deserving” couple’s infertility treatment. In this controversial advertisement, the commodified nature of babies was very directly acknowledged, even going as far as assigning them a cash value of prize money. However, more often the profit-oriented and consumer-driven nature of the infertility industry, although very real, is more subtle and not directly acknowledged.

The ways in which the patrons of the infertility medical-industrial complex function as “patients” and “consumers” are not distinct from each other, but are rather quite entangled. We can observe this entanglement of the medical and the commercial dimensions of infertility in its very definition, as established by American Society for Reproductive Medicine (the nation’s authority organization on reproduction and fertility). Despite being a purportedly medical definition, is quite evidently aimed at identifying clientele and potential consumers of infertility treatment:

“Infertility is the result of a disease (an interruption, cessation, or disorder of body functions, systems, or organs) of the male or female reproductive tract which prevents the conception of a child or the ability to carry a pregnancy to delivery. *The duration of unprotected intercourse with failure to conceive should be about 12 months before an infertility evaluation is undertaken (6 months if female partner is over 35 years of age), unless medical history, age, or physical findings dictate earlier evaluation and treatment.*”⁹⁶ [emphasis added]

We can see that the ASMR’s definition of infertility features two distinct age brackets.

⁹⁵ Griffiths, Sian. “‘Win a Baby’ Competition Criticised by Fertility Groups.” *The Guardian*, October 7, 2011, sec. World news. <http://www.theguardian.com/world/2011/oct/07/win-baby-competition-canada-radio>.

⁹⁶ “Infertility.” American Society for Reproductive Medicine. 2015.

What is interesting about this definition is that it differs between these brackets in a way that is contrary to what might be expected. As a woman ages and approaches menopause, her ability to conceive lowers as a result of the natural aging of her reproductive system, and so pregnancy becomes less likely. One would think, therefore, that an older woman should be permitted a longer amount of time to attempt to achieve pregnancy (perhaps 18 months compared to the 12 months given to women under 35) before being labeled as definitively infertile and targeted for infertility evaluation. However, this is not the case. Instead, women over 35 are recommended to wait only 6 months—less time than younger women—before seeking infertility evaluation. One can only assume from this peculiar distinction that the ASMR seeks to define infertility not only in terms a woman’s inability or unlikelihood to conceive (as might be expected), but also in consideration of the urgency of her seeking treatment based on a her remaining childbearing years. Apparently the concept of the biological clock is built into the very definition of infertility.⁹⁷ This is relevant to the infertility industry because its market consists only of women whose biological clocks have not yet run completely down. Indeed, we can see how this definition would make no sense at all in the absence of curative medical technologies like IVF. However, given the availability of these technologies, in the case of women who are on their last leg of reproductive years, it is important to draw them into the world of treatment before it’s too late. The definition of infertility supplies this force.

⁹⁷ Greil, Arthur L., and Julia McQuillan. “‘Trying’ Times: Medicalization, Intent, and Ambiguity in the Definition of Infertility.” *Medical Anthropology Quarterly* 24, no. 2 (June 2010): 137–56.

The validity of this definition has been called into question for being too inclusive and based on erroneous estimate of fertility decline, and therefore designed to designate a too-large body of patients. One study found that 34% of its participants would be considered infertile by ASRM's definition, as they had participated in more than one year of unprotected intercourse either with or without the intent to conceive a child.⁹⁸ Furthermore, the definition's age brackets have been criticized on the basis that the studies identifying the 35 years as the tipping point age of women's fertility declined are based on historical birth records, sometimes from hundreds of years in the past, which are not representative of fertility today. More recent studies have demonstrated that fertility decline after age 35 is much less significant than previously advertised.⁹⁹ So, the definitionally-designated 35-year warning on women's biological clocks might be unsupported. What is supported, however, is the fact that IVF is dramatically less effective in older women, largely because the pharmaceuticals used in the superovulation phase of the procedure have a decreased effect as women age and therefore fewer eggs are able to be extracted, fertilized, and transplanted. Because of this, older women have a lower overall pregnancy rate resulting from IVF.¹⁰⁰ In light of this, would make sense for

⁹⁸ Greil, Arthur L., and Julia McQuillan. "'Trying' Times: Medicalization, Intent, and Ambiguity in the Definition of Infertility." *Medical Anthropology Quarterly* 24, no. 2 (June 2010): 137–56.

⁹⁹ Dunson, David B., Donna D. Baird, and Bernardo Colombo. "Increased Infertility With Age in Men and Women." *Obstetrics & Gynecology* 103, no. 1 (January 2004): 51–56. doi:10.1097/01.AOG.0000100153.24061.45 and Rothman, Kenneth J., Lauren A. Wise, Henrik T. Sørensen, Anders H. Riis, Ellen M. Mikkelsen, and Elizabeth E. Hatch. "Volitional Determinants and Age-Related Decline in Fecundability: A General Population Prospective Cohort Study in Denmark." *Fertility and Sterility* 99, no. 7 (June 1, 2013): 1958–64. doi:10.1016/j.fertnstert.2013.02.040.

¹⁰⁰ Twenge, Jean. "How Long Can You Wait to Have a Baby?" *The Atlantic*, August 2013. http://www.theatlantic.com/magazine/archive/2013/07/how-long-can-you-wait-to-have-a-baby/309374/?utm_source=SFFB.

the industry to maintain an age-tiered definition with a relatively young cutoff that does not necessarily reflect age-related fertility decline such that women can be identified not before it is too late for them to have a baby, but before it is too late for them to use IVF to have that baby.

The “wild west” character of the infertility industry has had other lasting effects on the way that the economics of the industry have developed. Because highly privatized, unregulated, and free-market nature lead the treatments to be extremely expensive and the market space to be highly competitive. The average cost of one IVF cycle (including diagnosis, drugs, and surgical procedures) in the U.S. is roughly \$20,000.¹⁰¹ Only a fraction of states mandate any—and typically quite negligible—insurance coverage of these costs.¹⁰² These financial realities hold one of the keys to understanding how Lupron has come to be considered an indispensable component of IVF.

¹⁰¹ Uffalussy, Jennifer Gerson. “The Cost of IVF: 4 Things I Learned While Battling Infertility.” *Forbes*. Accessed October 17, 2015. <http://www.forbes.com/sites/learnvest/2014/02/06/the-cost-of-ivf-4-things-i-learned-while-battling-infertility/>.

¹⁰² This is not the case in many other developed nations. The Canadian province of Quebec covers the full cost of two IVF cycles. Statutory health care in Sweden covers the cost of up to three IVF cycles for women. Statutory health care in Germany covers 50% of the cost of up to three IVF cycles for women no older than 39. The U.S. and the U.K. are the only developed nations without universally mandated coverage of at least some of the costs associated with fertility treatment and IVF.

**100% REFUND FOR FAILED
IN VITRO FERTILIZATION**



PACIFIC FERTILITY CENTER, a leader in the field of in vitro fertilization, is proud to announce its Full Refund Plan (FRP). Here's how it works:

- ◆ You pay a single up-front fee* for all medically indicated services involved in a cycle of IVF whether it is with your own eggs, donor eggs, and/or IVF surrogacy.
- ◆ Couples with severe male infertility, including prior vasectomies, are also eligible.
- ◆ If you don't have a baby, you'll receive a full refund.

* Costs for drug therapy, egg donor and surrogacy agency fees, and services provided by outside physicians are not included.

Pacific Fertility Center can afford to offer this program because it has among the highest IVF success rates in America, and full confidence in its ability to get most patients pregnant quickly. Financing is available for qualifying patients.

**NOW ASK YOURSELF:
IF YOU NEED IVF, WHY WOULD YOU GO
ANYWHERE ELSE FOR TREATMENT?**

Call for detailed information, and to set up a free telephone consultation with a physician. Attend a free infertility seminar, where you'll learn more about the FRP, and the medical breakthroughs that have made it possible.

FREE INFERTILITY SEMINAR
Saturday, 11/15, 2:00pm
J.W. Marriott Hotel
5150 Westheimer Road at Sage
Across from the Galleria
Houston

888-TO PFC LA
888-867-3252
www.pfmc.com

Fig 5: an advertisement for the Pacific Fertility Center attracts customers with the guarantees of a baby “or your money back.”

As a consequence of the intense market competition of the infertility industry, clinics have been on a constant quest to increase the success rate of their procedures since the technology emerged. The mere 6% pregnancy rate reported by Edwards and Steptoe’s initial endeavors in the early 1980s had risen to a 22.3% success rates for all clinics by 1995 (this is the year Fertility Clinic Success Rate and Certification Act mandated that clinics begin keeping statistics).¹⁰³ In 2012, 44.4% of all IVF transfers resulted in pregnancies.¹⁰⁴ Clearly great strides have been made in increasing the likelihood that IVF will achieve its goal and clinics today continue to compete with each other for a scant percentage point, giving them an advantage over other clinics in an intensely competitive industry.

¹⁰³ Wang, Jeff, and Mark V Sauer. “In Vitro Fertilization (IVF): A Review of 3 Decades of Clinical Innovation and Technological Advancement.” *Therapeutics and Clinical Risk Management* 2, no. 4 (December 2006): 355–64.

¹⁰⁴ Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. “2012 Assisted Reproductive Technology Fertility Clinic Success Rates Report.” U.S. Department of Health and Human Services (Atlanta, GA, 2014).

Lupron has been a major contributor to the optimization of IVF protocols over the years. Lupron maximizes the efficiency of IVF by helping to induce a woman's body to produce an enormous number of eggs which can be harvested, fertilized in vitro, and transplanted for pregnancy. Therefore, the more eggs, the more likely this process is to be successful. A higher number of eggs also reduces the chances that a woman will have to undergo a second harvest, as she may be able to freeze some amount of embryos for a frozen embryo transfer at a later date if her first IVF attempt fails or if she wants to try for another child. Furthermore, a greater number of eggs means that prospective parents can have greater control over the quality of their offspring. Through technologies such as pre-implantation genetic diagnosis, information about embryos debilitating conditions and other health statuses can be learned and therefore parents can make the decision to pass up those particular embryos for implantation, choosing instead to attempt to become pregnant with only the healthiest, most desirable candidate embryos. All of these factors represent incentives for the use of Lupron from the perspective of the infertility client, particularly in light of the extreme out-of-pocket costs associated with IVF. So, too, do they represent motivations for the fertility clinician, who can take advantage of Lupron to increase the overall success rate of their procedures and thereby draw in customers by offering them the best possible chance of having a baby.

The cost-prohibitive nature of IVF and competition in the industry is captured perfectly in Figure 4, an advertisement for the Pacific Fertility Centers that was ran in a Houston newspaper.¹⁰⁵ Advertisements like this one are a testament to the extreme

¹⁰⁵ Winter, Catherine. "The Infertility Race: Competing for Customers." *American Public Media*, February 5, 1998. http://americanradioworks.publicradio.org/features/fertility_race/part3/section2.shtml.

lengths to which clinics are willing to go to attract potential patients. At this time several chains of clinics have adopted full- or partial-refund policies for the procedures they offer in an effort to gain a leg up over their competition by simultaneously assuaging potential client's financial worries while also emanating an air of infallible confidence in their methods. However, these policies frequently have strings attached. Patients often must meet certain criteria for these refund plans, with more challenging cases of infertility not qualifying for them. Some plans also do not include the cost of diagnostic tests or drugs, which can amount to nearly half of the overall cost of a cycle. However, even if they are in some ways too good to be true, these advertising maneuvers are undertaken on an increasingly wide scale as competition in the industry continues to stiffen, and have been very well received by infertile couples searching for ways to avoid becoming fraught with the crippling costs of infertility treatment.

SECTION V: LESSONS FROM LUPRON

The normalization of Lupron within the medical community and the public sphere is contingent on a set of factors that together produce the configurations and dynamics that support the normalization of drugs. These key factors and their significance are summarized as follows:

Key Factor #1: Part of the epistemic basis for the acceptance of drugs is an ethical tradeoff between risk and benefit. To be able to say that a drug is “safe and effective”

and therefore approved for public use is simply to say that it has met certain standards that were constructed by people. The decisions to establish those standards were based on systems of valuation. Thus, the FDA's "safe and effective" isn't some kind of objective, infallible stamp. It is obviously value-laden and therefore flexible under different circumstances where risk and benefit are variably balanced. The essential relationship is that threat of harm and level of risk are directly proportional: the greater the threat of harm, the greater the level of acceptable risk. At an institutional level, the fact that this relationship is dependent on circumstances can be observed in cases that deviate from FDA standards, such as "right to try" laws and the use of investigational Ebola drugs. Specifically in the case of IVF, regulators may be neglecting the potential of Lupron to cause harm because infertility is such a socioculturally-weighty, time-sensitive condition. Furthermore, the subjectivity of the risk-benefit tradeoff doesn't just manifest on a institutional level. Every day physicians and patients evaluate the risk-benefit tradeoff of drugs and treatments with their own personal discretion. When doing so, especially for certain conditions like infertility, they often draw upon sociocultural values. The incorporation of those values is often not visible in risk-benefit tradeoff analysis but is critical to understanding how and why drugs are assigned a certain level of potential benefit. In the case of Lupron, the sociocultural values built into the risk-benefit tradeoff are more clearly visible than in other cases, but the same principle demonstrated here can be extended to other drugs in order to understand their normalization.

Key Factor #2: The biomedicalization of infertility has created the conditions for Lupron to flourish by relegating childbearing difficulties to medicine. The impacts of this biomedicalization have served to guide infertile women's decisions toward the use of Lupron. First, the availability of assisted reproductive technology has created a renewed pronatalism in America and a neglect of other options like adoption and a childless lifestyle. Second, women who do choose to try to overcome their infertility are steered toward treating it with Western medicine as opposed to taking other approaches that may be approximately as likely to help them produce a child. Third, the way that women and couples make decisions about treatment is confined to the logic of risk-benefit assessment that is standard in American medicine, which leads women to shoulder more risks in order to achieve very value-laden concept of benefit. Lastly, the increasing industrialization of medicine means that the decisions made when undertaking infertility treatment are also based on market logic wherein childbearing and babies are commodities and the ability to obtain these commodities is reduced to a series of goods and services that can be bought and sold.

The third and fourth points in particular require additional elaboration. When a human status or condition is brought into the purview of medicine, those affected by it are invited (perhaps even compelled) to address and resolve that condition with medical solutions. When (bio)medicalization occurs, medicine becomes the dominant socioculturally acceptable approach to addressing the condition. This is in part because medicine is equated to science, evidence, and objectivity and therefore society considers it unwise, irresponsible, and even crazy to reject such things. However, the guise of

valueless-ness attached to medicine and science can obscure the co-constitutive relationship of medico-science and values. Although (bio)medicalization of a condition reshapes public values about how to approach that condition, the fact that the condition is designated as medically problematic can also be traced back to values. It is important to examine the co-production of medicine and values by extracting and interrogate the assumptions that were lost when a condition became medicalized and its treatments emerged in parallel. It is clear that these assumptions and values still comprise the basis on which individuals approach their treatment and the decisions they make, even when they are not explicitly acknowledged, and therefore hold a critical role in explaining how and why drugs come to be normalized.

Key Factor #3: The infertility medical-industrial complex is one that eschews regulation and oversight, largely as a result of historical factors (the long-standing rejection of IVF technology on ethical grounds by the establishment) and patient-consumers notions of reproductive rights and autonomy. This widespread absence of regulation means that there is a distinct lack of longitudinal record-keeping that would document health consequences for patients after they undergo IVF and treatment with Lupron. In addition, the privatized state of the industry leads to intense competition between infertility clinics and systemic lack of insurance coverage leads to extremely high out-of-pocket costs to patrons of the industry's services. These conditions allow Lupron to thrive because of the part that it plays in IVF, greatly increasing the number of eggs that can be extracted per cycle and thereby increasing pregnancy rate. Infertility clinics see

this as desirable because the ability to advertise high success rates is critical to a clinic's success in such a competitive market. Consumers see this as desirable because the ability to extract more eggs not only increases their chances of a cycle leading to pregnancy and decreases the odds of having to undergo a second, very expensive cycle; it also raises the possibility of freezing embryos for future transfers if the first round of implantations fails, which is a much less expensive option than starting IVF "from scratch." Therefore, financial conditions and market competition in the industry make Lupron an important (if not harmless) component of treatment. Although not officially endorsed by third-party health governance, the infertility industry has become an establishment in its own right and now operates with a set of uncodified norms, standards of practice, knowledge authorities, and social relations. It is under this regime that Lupron is embraced by the public and endorsed by medicine.

What can be learned more generally from deconstructing the case of Lupron in this fashion? First, the perception that a human status is problematic is a reflection of sociocultural values. When a problematic status comes to be considered medical in nature, the regimes of medicine reflect back on societal values and behaviors, changing the way in which that condition is approached. We can see this take hold institutionally in the regulation of drugs insofar as the type of risk-benefit analysis conducted by oversight bodies inevitably accounts for these values, as we can gather from Kathy Hudson's explanation of how lack of evidence in the realm of ART is balanced against the desperation of women whose biological clocks are running down. We can also

observe this co-constitutive relationship of medicine and values in the very way in which disease states are defined (as evidenced by the ASRM's definition of infertility, which is counterintuitively reliant on the existence of curative treatments simply to define the disease). Furthermore, zooming in from the institutional level, we see that the placement of a condition squarely in the domain of medicine has an impact on individuals' behavioral patterns as well. In particular, patients engage in a particular variety of risk evaluation and conceive of their personal rights and responsibilities differently as compared to decision-making outside of the context of medicine. In the case of infertility, gendered pronatalistic values run strongly through these notions of risk and responsibility and influence women's behavior and choices as they seek medical treatment. Furthermore, because medicine today is a commercial industry, the patient also acts as a consumer and is thus pursues treatment while being engaged in market logic wherein health products and services are considered commodities. This is especially true in the case of the highly privatized infertility industry. However, while "wild west" marketplace for babies appears lawless (and from the point of view of oversight, is officially so), its operations are in fact dictated by a system of uncodified norms (of which Lupron is one important, entrenched piece), including powerful notions of reproductive rights, unofficial standards of practice, and intense competition to acquire patients. The absence of regulation in the infertility industry makes it easy for us to see this system of uncodified norms, but even in regulated fields such a system still exists.

It is of these configuration and dynamics that Lupron has been deemed acceptable. At first glance, in light of its "bad drug" characteristics, the normalization of

Lupron doesn't seem to make sense. However, when we consider those characteristics in their appropriate contexts—socially, cultural, politico-economically, and institutionally—it becomes clear that the contradiction Lupron appears to present on its face is actually not a contradiction at all. Its normalization in the medical community and public sphere follows quite sensibly from the effect of several key factors. These key factors—including the value laden metrics by which decisions are made in drug regulation, the co-production of medicine and sociocultural norms facilitated by biomedicalization, and the market structures in which the drug and disease are embedded—represent an explanatory illustration of how one drug, Lupron, has become normalized. That Lupron has persisted in spite of itself and has overcome its classically “bad drug” reputation to be widely used and accepted is what makes the case a uniquely good candidate for inquiry on this level. However, at the same time, Lupron is not at all unique; for although Lupron is quite an easy case to read in these terms, the same terms can be applied to cases of other drugs. The key factors on which Lupron is contingent that I have described here are, to varying degrees, relevant to cases of other drugs as well, whether bad, good, or something in between. Thus, these lessons from Lupron are simply one important instance of many that are playing out in biomedicine at large today.

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