Is This Any Way to Have a Baby? - The terrifying truth about fertility drug

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Thousands of women are taking fertility drugs, but no one is telling them they're putting their lives on the line. We asked Barbara Seaman-the reporter who alerted the world to the dangers of birth control pills and hormone replacement therapy- to investigate the risks of pushing the reproductive envelope.

WHEN LOUISE BROWN, THE WORLD'S first test-tube baby, was born, in 1978, no one followed the news reports with more excitement than Liz Tilberis, then a 30 year-old fashion editor at British Vogue. After several years of trying to get pregnant, she and her husband, Andrew, had not been able to conceive.

Although Tilberis had been told repeatedly that she was simply working too hard, she consulted a London gynecologist who prescribed three cycles of Clomid, a workhorse of a drug that stimulates the ovaries (the doctor referred to it only as a "fertility booster). Clomid gave Tilberis stomach pain, bloating, breast tenderness, occasional vomiting, and hot flashes (she was spared the more serious side effects like severe dizziness and blurred vision); when it didn't get her pregnant, the doctor sent her to famed fertility surgeon Ian Craft, AID.

Craft performed an exploratory operation and discovered that both of Tilberis's falloplian tubes were blocked as the result of a sexually transmitted disease in her youth that had never been diagnosed. When he came to her hospital bed to tell her there was no way she was going to have children in her current condition. She later recalled in her memoir, No Time to Die, "I might have jumped out of the hospital windows if they hadn't been hermetically sealed.... That may sound shocking, but the psychology of infertility is pernicious and crushing."

Not long after, Tilberis underwent surgery to remove one ovary and fallopian tube and to clear the other temporarily, after which Craft invited her to become one of the original "test-tube tries" in his research clinic. She signed up instantly and began treatments while still sore from her operation. "In vitro, fertilization [IVF] was truly the stuff of science Action, something akin to cloning today," she would say, looking back. "Augmenting a woman chance to produce a viable egg with fertility drugs, then harvesting that egg and uniting it with sperm in a Petri dish certainly shared the public thrill that such a thing was possible."

Each month on the 11th day of her cycle, already swollen with Clomid and a second drug, Pergonal, and teary from their pharmacological effects on her emotions, Tilberis entered the hospital for her egg extraction. In rapt fascination, she watched the eggs "ready to burst out of their follicles" on an ultrasound screen, then was hurried into the operating room and given general anesthesia. The doctor made two incisions, one just below her belly button for the laparoscope to enter and locate the eggs, the other above her pelvic bone to accommodate the syringe that would aspirate them (these days egg extraction can be done with a local anesthetic). Only once did these efforts result in a Petri dish fertilization. Tilberis was rushed to the hospital, where the embryo was inserted into her uterus. But it turned out to be a "chemical pregnancy" -hormones surged but the egg didn't implant and it quickly ended in a heavy bleed. That fleeting embryo was the closest she came to the experience of giving birth, and she deeply mourned the loss.

After nine debilitating cycles, Tilberis adopted two dearly beloved sons, Robbie and Chris, and fast-tracked her career to become a distinguished editor in chief.

Life was good. She and Andrew still adored each other. And she was doing so well at British Vogue that in January 1992, American Harper's Bazaar stole her away and brought her to New York. But less than two years later, in December 1993, she was diagnosed with advanced ovarian cancer. Her doctors suggested that her history of fertility treatments might have put her at a higher risk. She learned that Gilda Radner, the comedian who died of ovarian cancer at 42, had also taken fertility drugs. Radner's husband, Gene Wilder, had given her the shots of Pergonal himself after practicing on oranges and grapefruits.

"Being told I had cancer was not as hard as being told I was infertile," Tilberis said, but she demanded to know if there was a connection. "The unanticipated question that most affected my life was, What might this pushing of the reproductive envelope be doing to my ovaries?"

LOUISE BROWN, NOW A POSTAL worker in Bristol, celebrated her 25th birthday this past July. And today fertility treatments are taken lightly, so much a part of our landscape that they're constant fodder for sitcoms like Frasier and Friends.

But as the industry thrives at $2 billion a year, reproductive medicine is in many ways a wild Wild West where doctors can practice like cowboys, using drugs that haven't been approved for fertility, and where no one is regulating the clinics, which often boast inflated success rates. 'A fertility doctor can literally set up a lab in his garage and hire his son or daughter to run it, and it would be perfectly legal," says Brooks A. Keel, PhD, professor of biomedical sciences and associate vice president of research at Florida State University. 'A woman gets more regulatory oversight when she gets a tattoo than when she gets IVE"

Surprisingly, although the Clinical Laboratory Improvement Amendments of 1988 set strict quality control standards for medical laboratories, facilities that deal with women's eggs are exempt. Senator Ron Wyden of Oregon, who has steadily pushed for regulation of the fertility field, managed to get a bill pass in 1992 requiring that clinics at least report accurate success rates. But today some facilities notoriously cook their books to show the kind of success rates that will attract new patients. And Wyden himself acknowledges, "There is no question people still get around the law." By many accounts, government agencies like the Food and Drug Admimstration (FDA) and National Institutes of Health (NIII) are looking the other way-fallout, perhaps, from politicized controversies over stem, cell research and frozen embryos.

As almost any woman who has gone the fertility route knows, these treatments are often painful and always costly, and only one in four who attempt a test-tube pregnancy will take home a live baby, according to the best data available – odds that plunge to 5 percent at age 43 and only 2 percent after that. The grueling nature of even a single cycle is hard to grasp.

"when I was on Gonal-F and Repronex, my abdomen so swollen from the egg follicle production that I had difficulty breathing," says a woman named Mona P. Who eventually did get pregnant with twins. "I gave myself subcutaneous injections in the stomach, and my husband gave the intramuscular injections in the hip. 1 hate needles. The night of egg retrieval, you take progesterone shots, which are extremely painful and create lumps under your skin. After retrieval my ovaries filled up with fluid, so 1 kept the uncomfortable bloated feeling for another three or four weeks. A horrible pain in my left shoulder lingered on and on. In all we paid $20,000 to the clinic including about $4,000 for the drugs."

Beyond discomfort, assisted reproductive techniques pose serious health threats like ectopic pregnancy (embryos may migrate or be inadvertently misplaced), and more than one out of three IVF deliveries are multiple births (which often result in childbirth complications and severe infant health problems). And it isn't just die physical trauma that lays women low, says Harvard professor Alice Domar, PhD, director of the Mind/body Center for Women's Health at Boston IVE It's also the rising disappointment with each treated cycle where hopes are raised, and then dashed.

Without oversight of fertility clinics, many patients go through harrowing ordeals for nothing. I talked to some women who got the full monty of ovulation hormones when - they would later find out their husband's sperm was solely the problem, and others who were pumped with drugs before doctors realized their misshapen uteruses could never carry a fetus. In the absence of regulation, too, a rogue doctor is more likely to have free reign.

FAMOUSLY, IN 1995, RICARDO ASCH, MD, at the University of California at Irvine, was accused of filching his patients' fertilized eggs to place in other women's wombs. And he was considered one of the best in the field-the man who invented GIFT, a technique in which the egg and the sperm are placed in the fallopian tubes and fertilized within the woman's body (the license plate on his Ferrari read DR. GIFT). Asch was indicted but fled to Mexico. Another hallowed specialist, Cecil Jacobson, AM, who ran a clinic in Tysons Corner, Virginia, was convicted in 1992 on 52 counts of fraud and perjury- and sentenced to five years -for performing "anonymous donor" fertilization, using his own sperm, in as many as 75 patients.

But even with the best doctors and most sterling clinics, there are still glaring gaps in our knowledge about the danger fertility drugs may pose and whether the benefits outweigh die risks. A leading fertility scholar who prefers to remain anonymous minces no words: "This is a field that thrives in the absence of factual information. There is little work on animals to show safety or randomized clinical trials to compare results. We make the same mistakes, but with increasing confidence."

LIZ TILBERIS DIED OF HER CANCER at 51, in April 1999, having revitalized Harper's Bazaar and presided over the Ovarian Cancer Research Fund. But her question about the connection between ovarian cancer and fertility treatments remain unanswered, the necessary clinical trials yet to materialize.

In truth, it would take a brilliant scientist to devise a study capable of teasing out the individual drugs from the pharmaceutical stew many patients now end up taking. (Mona's list included "11 vials of Repronex, 33 powders of Gonal-F, one order of Profasi, a month's supply of Lupron, nine days of Doxycycline, and two Valium") But the major drugs of concern in terms of ovarian cancer are those that induce ovulation, like Clomid, the typical first step for most infertile women, and Pergonal, which increases the number of eggs produced, and is often the second. Both were discovered in the 1950s, and for some infertile women, they're wonder drugs. Pergonal (human menopausal gonadotropin) is extracted from the urine of postmenopausal women and must be given by daily injection into the muscles of the buttocks or thighs. Clomid (clomiphene citrate, also sold as Serophene) can be taken orally. It is derived from DES (diethylstibestrol, the infamous synthetic estrogen given to pregnant woman for 30 years before it was found, in the 1970, to cause a rare form of cancer in their daughters, as well as birth defects like T-shaped uteruses and other anatomical distortions that make it difficult, if not impossible, to carry a baby.

Scientists theorize that the more often the ovaries are stressed by going through a monthly cycle ending in the rupture of an egg, the more prone they are do damage and to the development of abnormal cells that could become cancerous. Pregnancy and breastfeeding give your ovaries time off, and as a result, each child you have lowers your risk of ovarian cancer by 10 to 15 percent. Birth control pills, which suppress

ovulation, are also known to decrease the cancer's frequency Using this logic, hyper-ovulation caused by fertility drugs like Clomid and Pergonal would mean a higher risk.

In the early 19gos, two major studies linked such drugs to the occurrence of ovarian tumors, although in both case the lead authors felt they had only shows enough evidence to warrant further investigation. Other studies failed to find connection. In 2000, however, the well respected Cochrane Collaboration, a independent organization that conduct reviews of medical studies, conclude that adverse effects of Clomid "include a possible ovarian cancer risk." Serono agrees that the relationship between it drug Serophene and ovarian cancer is

"controversial" (the company also states that no causal link has been established for Pergonal). Dennis Marshall, PhD, executive director of medical affairs at Ferring, another fertility drug maker, notes that while there's no final answer on ovarian cancer, doctors are now using lower doses to stimulate patients' ovaries.

Whatever the risk is, shamefully, we do not yet have a handle on it. Last spring I received a letter from John Coffins, MD, professor emeritus of obstetrics and gynecology at McMaster University in Ontario, who was an author of the Cochrane review and is considered an experienced evaluator of ovarian cancer studies. "The risk is not one that would be considered proven," he wrote, "and the subject does not seem to have had a high priority for further research in the last few years-" Some new research, however, may be emerging, aimed at identifying particular women with genetic susceptibilities to ovarian cancer for whom drugs like Clomid could be dangerous. Two case reports published in The New England Journal of Medicine last August do "point to a potential subgroup of patients who could be at risk of harm due to ovulation-stimulant therapies," says Ursula Kaiser, MD, at Brigham and Women's Hospital in Boston, author of an accompanying editorial.

Whether Diane Leatherman was in this group or not is unclear. But the 66 year-old nonprofit consultant and author (Crossing Kansas, a fictionalized memoir, and Rebecca: A Maryland Farm Girl, a Children's book) was diagnosed with ovarian cancer about 18 years after she took Clomid and Pergonal. (This was basically Tilberis's time frame, too.) Leatherman already had four children when, at age 40, she fell in love with her third husband. They decided to try for another child. After several rounds of the drugs, she got pregnant the natural way and one month short of her 48th birthday delivered a baby girl. When Leatherman was diagnosed with cancer, the oncologist asked about her history of fertility drugs. "Any time you go splitting cells, you can run into trouble," she recalls him saying. Today her ovarian cancer has spread to her brain. Her doctor has suggested she get her affairs in order.

Leatherman urges all women who have had ovulation treatments to watch out for signs of the cancer (thickening of the waist, feeling full after eating only a little, changes in

bowel movements, pain during sex). Despite the haunting questions about its dangers, Clomid remain as one of the most commonly prescribed fertility drugs in the country As a couplet scribbled on the bathroom wall of a California fertility clinic puts it, CLOMID: WIDELY USED, MUCH ABUSED.

THE JOURNAL FERTILITY AND STERILITY published an NIH study last year showing that women who took human menopausal gonadotropin (Pergonal-type drugs) for at least six cycles had a risk of breast cancer two to three times greater than women who had never used fertility medication. The findings are very tentative, but a few experts believe that breast- more than ovarian -cancer may emerge as the real concern.

Cancer, however, is not the only cloud hanging over high-tech babymaking drugs. Any potential patient would think twice if she had sat next to Suzanne Parisian, MD, when this former FDA official who wrote FDA Inside and Out studied the file of agency records on Lupron A synthetic hormone that suppresses the pituitary gland, Lupton is often prescribed to both infertile women and egg donors to control the timing of ovulation. The drug, however, was never approved for this purpose. After writing a 100 page report, Parisian sent me a note: "Lupton is approved for only two short-term applications in women, (a) preoperative treatment of fibroids in patients with anemia and (b) management of endometriosis for a limit of six months. The FDA never approved Lupron for more than six months because there is significant risk of irreversible bone loss." Prescribing drugs for an unapproved, or 'off-label,' use is legal and quite common in medicine. But patients should be informed when it happens. And some women, especially "frequent fliers," who go through many cycles hoping for a baby-get more than the FDAs limit.

Parisian goes on to say that Lupton produces a postmenopausal state in women ("It literally drops the floor right out from beneath them without anytime for the body to acclimate to the hormonal change"). Perhaps most alarmingly, she writes, far from being approved for fertility, Lupton "is 'pregnancy category X,' which means it is labeled not to be given to women intending to become pregnant or already pregnant .... The entire IVF field uses, Lupton for physician convenience. It lets them plan when to do [egg] harvests at a comfortable hour for them. They bully women into using it, telling them that there will be an increased risk of failure without Lupron There is absolutely no real science to using Lupton for IVF."

Another concerned physician, Susan C. Vaughan, MD, a psychiatrist and pharmacology expert, has had two successful IVF babies, financed by the best-selling book she wrote, Viagra: A Guide to the Phenomenal Potency-Promoting Drug. Acknowledging that ovarian cancer may turn out to be more of a worry than she originally thought, Vaughan has taken a special interest in treating patients who suffer from anxiety and depression after going on fertility drug. She charges that too many fertility doctors "underestimate how rotten people feel on Lupron They'll advise, 'At yew age, you

should have such and such a dose, 'but they don't consider the emotional effects. A woman who did well on two and a half vials of Pergonal cried hopelessly when she was given six of these injectables." Vaughan adds that the doctor and the patient may both push the envelope too hard, desperate to have die treatments work before the money-as much as $20,000 per cycle, with some patients spending $150,000 for six cycles-runs out.

Complaints about Lupton go well beyond mood swings. A small percentage of women, it seems, never recover from what was supposed to be a temporary pituitary shutdown. At least one lawsuit filed on behalf of five Florida patients who took Lupron - for endometriosis and infertility- alleges that the drug causes chronic physical distress, TAP Pharmaceuticals denies liability for all the charges.

More than a dozen women interviewed for this story, however, went on record to report a litany of medical complaints they believed to be the result of Lupron Among the more common: autoimmune diseases, neurological problems, stomach disorders, and severe unexplained pain. Marriages fell apart. Careers languished. "We've gone to what seems like 5,000 doctors," laments the husband of one woman who at 25 was put on Lupton to help her get pregnant (she's since been hospitalized for chest pain and extreme hives, and suffers from a battery of other ailments). "They say, 'think of something that might have caused all these things to suddenly come about.' And I tell them, 'Yeah! She took Lupron and she's been sick ever since.' But they say Lupton doesn't have anything to do with it. I'm watching my wife fall apart in front of my eyes, and no one wants to do a thing about it."

One woman trying to do something is Lynne Milican, 46. A registered nurse, she has also become a paralegal and a knowledgeable activist on the dangers of Lupron. Last year, as part of her ongoing efforts to get the government to investigate, she testified before Congress on behalf of thousands of women who have reportedly been harmed by the drug.

Millican's own story began at age 32, when she started the first of three IVF cycles. She was already taking Lupton for endometriosis, and her doctor continued giving her the drug. He neglected to mention that it wasn't approved for fertility treatment. In the 14 years since taking Lupron Mallican has had 22 hospitalizations, and her problems have included a large, benign tumor in her gallbladder, which appeared a few months after the I VF; severe fatigue; and gastroparesis (paralysis of the stomach and intestines). Her medical history typed out, single-spaced on a continuous ream of paper- stands seven and a half feet tall. One condition that never made it onto the list is pregnancy.

"I think every physician who uses Lupron has seen some scary things, and they're not sure if it's due to the Lupron says Michael Zinaman, NID, who readily prescribes the drug for endometriosis and infertility, warning patients of possible negative effects. "I get calls saying, 'Have you ever heard of women taking Lupton and having this, this,

and this?'" Zinaman, a professor of reproductive endocrinology and the head of Loyola University's fertility program in Chicago, believes 2 or 3 percent of women using the drug have "really bad things happen to them." David Redwine, MD, a gynecologist at the St. Charles Medical Center in Bend, Oregon, has treated hundreds of endometriosis patients, many suffering from adverse reactions to Lupron, but says that, unfortunately, there are no studies tracking the long-term effects,

THE PUSH FOR EFFECTIVE FERTILITY drugs has been fierce, fueled by the promise of pharmaceutical profits and by the collective ticking of America's biological clock, set ever later for having children, In 1970 Pergonal was still under study. That was the year that one volunteer, Margaret Kienast of New Jersey gave birth to quintuplets. The publicity made infertile women frantic with hope, In Los Angeles Edward Tyler, MD (who happened to write for Groucho Marx on the side), had tried it on 300 patients but was still reluctant to recommend it for general use.

The manufacturer, Cutter Laboratories, also believed the publicity was premature. One month after the Kienast births, the clinics testing Pergonal were booked solid and Tyler announced, "We don't have a vial in the house." Despite the hesitation of both the researchers and Cutter, the drug was approved that same year.

Today Pergonal has spawned a number of offshoots, including Humegon, Fertinex, Repronex, Gonal-F, and Follistim. In a recent inter-view, New Jersey fertility specialist Satty Gill Keswani, MD, (also a United Nations NGO delegate studying the environment's impact on fertility) described a close relative's near brush with death from a reaction to one of these ovulation drugs.

After trying to get pregnant for two years, Keswani's 34-year-old relative, "Danielle," was diagnosed with endometriosis. "Everything was okay except that one of her fallopian tubes was problematic," Keswani told me. She did not want Danielle to go ahead with IVE "With one healthy tube, and being under 35, she still had a good chance without it," she said. "But many doctors press younger women to do IVF to increase their success numbers." Keswani does refer some of her own patients for IVF but notes that for those who fail after several tries, "it takes months to get the drugs out of their bodies."

Keswani was attending a medical meeting in San Diego when Danielle, who had been on the ovulation drug for ten days, telephoned in tears. She had a pseudo

tumor in her brain. "This is a swelling that appears to be a tumor," Keswani says. "I ran for a plane and got home at 3 A.M. We did an MRI of her brain. The accumulated fluid of the pseudoturmor had to be removed by spinal tap. I asked Danielle's doctors to stop the drug and showed them studies that it can cause blindness. The spinal fluid pressure

was 480, when normally it would be 250. Her doctors, all men, wouldn't listen to me. They didn't want to 'interrupt the cycle' and let their treatment go to waste.''

About 5 percent of patients taking this family of drugs develop hyperstimulation syndrome, which often involves the rapid enlargement of the ovaries and can be fatal. Fluid typically accumulates in the abdomen and sometimes the lungs, cutting off the breath; if the ovary ruptures, blood also pools and clots can occur. With Danielle, who fortunately survived, the excess fluid collected in the optic nerves.

Two days after her spinal tap, doctors removed nine eggs, and when they had two or three embryos, they implanted them into her womb. It didn't work. "She was so down," Keswani tells me, "and it took three months for her eyes to clear up from the swelling of the nerves." But the story had a happy ending. Danielle and her husband went on vacation to Italy, says Keswani, "and they came back pregnant-the good, old-fashioned way."

IF THE RISKS OF FERTILITY DRUGS and treatments aren't clear, neither are the benefits, Add desperation for a child to the mix, and infertile women are in a difficult spot when it comes to making an informed choice about going high-tech.

Medical sociologist Joan Liebmann Smith, PhD, a former board member of the patient advocacy group Resolve, calls the examining table where IVF is done "the gaming table" because when you go for treatment, you are literally taking a gamble. The real odds of taking a baby home, however, remain elusive. Even when clinics don’t blatantly inflate their success rates, the industry is rife with a more subtle kind of manipulation that skews the final numbers. Ninety-three-year-old Howard Jones, MD, who co-founded the Jones Institute for Reproductive Medicine of Eastern Virginia Medical School, points out that busy clinics bent on posting stellar rates are apt to turn away die harder cases. Jane Miller, MD, a fertility doctor in New Jersey, agrees that smaller facilities and solo practitioners have a difficult time cracking the high numbers if they welcome the big clinic rejects. The Society for Assisted Reproductive Technology tracks success rates of clinics for the Centers for Disease Control and Prevention (results can be seen at cdc.gov). But these figures, by and large, depend on the accuracy and honesty of the self-reporting clinics - most of which are the society's members.

Whether a woman needs help conceiving in the first place isn't always obvious. When she goes in for a workup the specialist may have little incentive to send her back to the drawing board, or bed, as the case maybe. "Bear in mind that if you wish to develop a reputation as a fertility doctor, you don't want patients getting pregnant on their own," as one insider puts it. Last May the Medical College of Georgia's distinguished authority Paul McDonough, MD, speaking to a group of New York and New Jersey fertility specialists, urged his colleagues to "go after the low-hanging fruit," meaning the obvious causes of infertility- sperm problems, fallopian tube injuries (from STDs and

abortions), and genetic or prenatal conditions -before they pull out their prescription pads. Prospective patients might also consider patience, Some research shows that couples up to their mid-30s with no evident infertility factors have a better chance of success if they simply continue on their own.

The answers to all these questions will come one day. But for now, one can only proceed with extreme caution. For all the promise that reproductive medicine offers to those who dare to cross its threshold, with all the great joy it brings to a relatively small number of lucky seekers, it also breaks many hearts and bears risks that are yet unknown. In The Empty Cradle: Infertility in America form Colonial Times to the Present, two sisters, historian Margaret Marsh, PhD, and gynecologist Wanda Runner, MD, wisely write, "Infertile women have served as both patients and experimental subjects." And for every one of us who follows in the footsteps of Liz Tilberis, that is still very much the case.

With reporting by Joanna Perlman, a researcher and writer in New York City.