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Boston Women's Health Book Collective
Update Committee

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Dear Update Committee:

After re-reading Chapter 18, the 'New Reproductive Technologies' chapter, I was struck with the lack of mention of the health risks associated with these technologies and the fertility drugs. The concerns that are raised in the chapter (the invasiveness and manipulation of women's bodies, and the political, social and economical impact), I believe, cannot properly be discussed without first addressing the short and long term risks (both the known, suspected, and unknown) that are associated with these procedures and drugs.

I've made some comments and addenda to the chapter itself, but since there is an incredible amount of information, I'm also enclosing a smattering of information gleaned from the medical literature. This broad sampling addresses the negative side of reprotech, the side the consumer, to date, has barely had a glimpse. Hopefully the Committee will find this information useful and pertinent to the update.

Since 1992, many issues and a growing number of different procedures have evolved in the field of reproductive technologies. Even though "present scientific evidence *does not support* the use of IVF for indications other than tubal blockage" (Buitendijk, 1995, p.901), and despite the lack of safety and efficacy data ... the indications for IVF and it's variants have exponentiated (endometriosis, subfertility, polycystic ovarian disease, unexplained infertility, *male* factor infertility, egg donation, surrogacy, preimplantation diagnosis, postmenopausal pregnancies, or simply to verify that fertilization takes place). There is a dizzying array of acronyms for the ever-expanding procedures: there's IVF, GIFT, ZIFT (zygote intrafallopian transfer), TET (tubal embryo transfer), FET (frozen embryo transfer), ICSI (intracytoplasmic sperm injection), SUZI (subzonal insertion), DIPI (direct intraperitoneal insemination), ICI (intracervical insemination), ITI (intratubal insemination), IUI (intrauterine insemination), SFR (selective fetal reduction).

Just in the last four years, for the first time in history: There have been virgin births; *abnormal* human embryos <u>have been transferred</u> into women undergoing IVF (Munne et al., 1995); fertility drugs are bought and sold over the internet (without benefit of prescription); fertility clinic solicitation of egg donors has become commonplace; human embryos have been cloned; and the possibility to transplant aborted fetuses' ovaries into women has emerged. One could bear one's own brother, or be the offspring of an unborn non-person. Human embryos are being grown in human ovarian-cancer cells (Ben-Chetrit,.et al., 1996), among other substances, for research, and embryonic kidney cells have been used to make recombinant DNA fertility drugs. The 1994 National Institutes of Health's Human Embryo Research Panel Hearings stated that there is much profit to be made in embryo research: "Therapeutic agents, vaccines, hormones, proteins, stem cells, gene therapy, cell lines, chimeras, patents" - all are potential products of embryo research (which cannot begin without eggs). A current goal is to mature oocytes in vitro, controlling in the lab the very development of eggs - rendering the woman dispensible to this process.

But while the many procedures, drugs, devices, and tests have been increasingly used on women, there has been a lack of informed consent provided to the women regarding the risks. "(E)vidence exists that there has been less adherence to appropriate disclosure of information by practitioners of assisted reproduction than is ethically required" (Macklin, 1995, p.486), and "at some centers, incomplete and misleading information is given to women" (Baird, 1995, p.494). "Physicians and the pharmaceutical industry are making huge profits treating infertility, and hyperstimulation drugs are central to their limited success in producing healthy infants. A powerful incentive exists to overlook or downplay any bad news." (Napoli, 1994, p.6).

John A. Robertson states: "As more personnel become involved in handling gametes and embryos, the number of embryos lost because of negligent handling or accidents in the laboratory may increase. Often couples may not learn of these mishaps, but be told that "oocytes did not fertilize," that zygotes "did not cleave," or that "your embryos were not viable". ... Internal pressures to cover up errors should also be resisted." (Robertson, 1996).

Ovarian, breast, and endometrial cancers, visceral and vascular injuries, adverse neurological symptoms, memory complaints, bone loss, infections, and death are but a few of the known risks associated with fertility treatment and/or fertility drugs. Bacterial contamination following egg retrieval (transvaginal aspiration) "appears to occur commonly" (Saltes, 1995, p.658). Transvaginal oocyte aspiration is associated with varying degrees of bleeding and the risks of infections, visceral trauma, and risk of injury to blood vessels; and the trauma of puncturing follicles may interfere with the formation of functioning corpus lutea - one potential cause of the low pregnancy rates (Bequaert Holmes, 1988). Studies in mice who were administered superovulatory hormones developed malformations which was "transmittable to subsequent generations", and in human IVF embryos, a "higher than expected number of structural chromosomal anomalies" have been noted. (Kola, 1988, p146). "That superovulation is a problem that results in many abnormal embryos in universally recognized in animal breeding." (Moor, etal., 1985, p171)

Ovarian hyperstimulation syndrome (OHSS), in some degree, occurs in *all* women undergoing treatment with hMG/hCG (Golan, et al., 1989; Forman, et al., 1990). The incidence of mild OHSS has been found to be up to 23%, moderate OHSS up to 7%, and severe OHSS (which is life threatening) has been found in several studies to occur in up to 33%. The mild form of the syndrome with clomid has been found to have an incidence of 8%. One Clomid/hCG woman developed the syndrome 7 weeks after ovulation. (Golan, 1989).

"Assisted reproduction practice should be well controlled in view of the potential for complications before and during pregnancies. ... Medical complications are an indispensable aspect of every discussion dealing with ovulation induction, or IVF-ET, GIFT, and ZIFT (Schenker & Ezra, 1994). "Chromosomal aberrations have been reported in about 60% of natural cycle abortions and an increased rate (83%) has been noted in patients undergoing ovulation induction. However, there are limited data on patients undergoing assisted reproduction." (Shields, et. al., 1992).

Pregnancy rates are lower when using high doses of exogenous gonadotropins, and there may be a detrimental effect of the high E2 milieu on oocyte and/or endometrial quality. ... Histologic analysis of the endometrium has shown altered maturation in response to ovarian stimulation ... suggesting that ovarian stimulation may affect the secretion of certain growth factors needed for implantation and early growth of the embryo." (Stadtmauer, et. al., 1994, p1063).

While there appears to be a lack of informed consent regarding the risks of fertility drugs and treatment, these risks were openly discussed at the 1994 National Institutes of Health Human Embryo Research Panel Hearings. Dr. Van Blerkom, reporting the 'State of the Science of Human Embryo Research: "To IVF methodologies and techniques ... there are procedures done that I think a lot of you would consider experiment that are in clinical use. They have received no oversight, they have received no real evaluation. They're just done. This field is based on methodologies being introduced

into clinical practice based on a few papers, based on a few studies, based on exchanges of information at meetings, without a thorough evaluation." (Van Blerkom, 1994; p. 77). Panel member and Doctor of Philosophy, Carol A. Tauer: "I think we need to say something about the detrimental things that have occurred in the last 15 years, the fact that clinical work has gone on without the basic science to underlie it... I think the fact that research enterprise has gone on out there without peer review and without the appropriate safeguards is something very bad that has happened." (Tauer, 1994, p.54).

Women should pay particular attention to the issue of egg donation. As many as 91 eggs at one time were taken from one woman who was undergoing superovulation! While that number is extreme, the goal is to *get as many as possible* ... and women should be asking why is there such a demand for so many eggs. The fertility journals are rife with article after article using 'donor eggs' in research - if there is such a shortage, how is it that so many tens of thousands are available for 'research' ... and how would the healthy women who donates eggs "to give the infertile couple the child of their dreams" feel if her eggs were destined only for a lab?

Fertility clinics frequently target the young, healthy, fertile women for egg donation through college and parenting newspapers, and pay the woman up to $2000 and more for one round of hormonal stimulation and egg retrieval. The woman usually undergoes some form of psychological testing, in contrast to sperm donors who require no such psychological testing. One Boston fertility clinic advertises that it is located on the train line - an enticement for the economically disadvantaged women without means of transportation. There has been an estimated 200,000 frozen embryos in the world, while the demand for eggs is high and growing. There have been scandals of eggs stolen - at the University of California, Irvine, the inventors of the GIFT procedure, Drs. Asch and Balmaceda, have been charged with covertly using the eggs of women without their permission, and selling them to women as donor eggs (Kelleher et al., 1995). In a Rhode Island hospital fertility clinic, it is likewise charged that eggs were stolen and either sold to unsuspecting women or used in research. The inventor of amniocentisis, Dr. Cecil Jacobson, was found guilty of substituting his own sperm for that of the woman's partner, and fathered over 75 children. (And a Dutch couple undergoing IVF gave birth to twins, one black and one white - because the clinic had reused a pipette from a previous cycle, introducing two man's sperm to this woman's egg.).

"Current evidence indicates that most patients who donated oocytes during their own cycle of IVF treatment did not conceive" (Shenker, 1995, p.501). Regarding post-menopausal pregnancies, "a close study should be made on maternal morbidity, since some clinics report a high frequency." (Flamigni, 1995, p.16S).

Daily subcutaneous injections or nasal sprays of gonadotrophin releasing hormone agonists (GnRH-a) are commonly utilized in a fertility cycle - the most frequent method used is daily lupron injections. Monthly injections of GnRH agonists have also been given. GnRH agonists are classified by the FDA as "Pregnancy Category X drugs", meaning "studies in animals or human, or investigational or post-marketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient" (Physicians Desk Reference [PDR], 1994,). Lupron, the most common GnRH agonist used, is known to "shut down blood flow to the frontal lobes of the brain" (Hale, 1994); and "1/600th the human dose causes major fetal abnormalities in rabbits when administered on day 6 of pregnancy" (PDR, 1992 - 1996). Lupron, according to de Haen's American Hospital Formulary Service Therapeutic Classification System (de Haen, 1985), is classified as an "antineoplastic/other" (as is Interferon Alpha-2A&B) and is not classified as an "antineoplastic/hormone" (as is tamoxifen). A man with prostate cancer which has spread to his bone is routinely prescribed 3.75 mg of Lupron per *month* as his antineoplastic treatment... a woman undergoing IVF will be prescribed 1-2 mg of Lupron per *day* from two weeks to over a month, commonly receiving *in excess of 20 mg of Lupron in one month.*

It has been noted that during GnRH agonist treatment, "ovarian cyst formation occurs ... the consequences of which are unclear" (Deidrich et al., 1991). "In humans, few experiments have been conducted on the biological action of GnRH agonists, with contradictory results." (Guerrero, et al., 1993). GnRH-a/hMG "oocytes are of lower quality than those retrieved from cycles using hMG alone". (Stadtmauer, et al 1994). "Lornage et al. have reported a rise in the percentage of embryos with <50% intact blastomeres when using the leuprolide acetate-hMG protocol." (Benshushan, et al., 1993, p. 1066). "Identification of GnRH binding sites in tissues outside of the reproductive tract suggest that leuprolide [lupron] may have actions previously unsuspected. ... further investigation of GnRH agonists mechanisms of action are essential in view of the increasing clinical uses." (Blacker, et. al., 1991, p587). "... (A) substantial majority of the patients [72%] showed difficulty with memory while on leuprolide acetate" (Varney, et al., 1993; p.57) ... and "memory disruption may be a more common side effect of GnRH-a treatment than currently is recognized." (Newton, et. al., 1996, p.1253).

"Lupron embryos were different. They grew faster, developed more rapidly. They were more fragile when frozen and less likely to survive thawing. Nobody knew why or what it meant for the long-term health of the woman or any resulting child." (Hotz, 1991). In a study examining women undergoing fertility treatment who had inadvertently conceived while taking lupron, there was a 43.5% incidence of adverse pregnancy outcomes (Karande et. al., 1996). Keenan et al. "demonstrated that the development of embryos after suppression with GnRH-a was accelerated. This phenomenon interfered with the cryoprotectant qualities ... Given the important role of cryopreservation in IVF, any demonstrable adverse effect of GnRH-a on the efficiency of this process may have major implications on its use in ovulation induction for assisted reproductive techniques." (Benshushan, 1993, p.1066),

Lupron is *not* FDA approved for the indication of fertility treatment or in vitro fertilization. One renowned Boston fertility doctor stated that "women do not need to know about the lack of FDA approval" (Kong, 1996). According to the 1989 and 1990 Annual Reports of Abbott Laboratories, which manufacturers Lupron, "clinical trials for lupron's use in in vitro fertilization and fertility treatment are underway". However, "clinical studies for Lupron's use in treating infertility have been discontinued" (Abbott, personal correspondence, 1995)... why were these trials discontinued? And why are 90% of fertility clinics using tested but never approved GnRH-a in fertility treatment? There are thousands of women who have experienced health problems after taking lupron. In Collingswood, N. J., two dentists (who are sisters) founded 'The National Lupron Victims Network' (NLVN) [P.O. Box 193; 609-858-2132: web site; http://www.voicenet.com/~nlvn]. The NLVN is an informational, support, and research network which is collecting and disseminating data on the published (but often under- or un-reported) adverse events following exposure to lupron.

Another addition to the fertility drug regime is the GnRH antagonist... small scale studies of 'Volunteers" at IVF programs are now receiving third generation compounds, that "although these results need to be confirmed by larger, randomized studies", there is a "bright future" for these compounds. Dexamethasone, heparin, aspirin, Robitussin, albumin, immunoglobulins, and other assorted drugs, agents, and compounds are used for various purposes in a number of fertility cycles (of course, the true "number" of any such 'trial and error' combination remains unknown!).

Since no long term studies were required before FDA approval of Clomid and Pergonal in 1967 and 1969, respectively, "today, nearly 30 years later, methodologically sound research is still lacking" (St. Clair, 1991). Clomid has been associated with testicular cancer, ectopic pregnancy, and ovarian cancer (Leikin, 1996), and is chemically similar to DES. Drug firms, at the FDA's request, are revising fertility drug labels to include ovarian cancer as a potential adverse drug reaction. ... Since fertility drugs were first marketed, at least 12.5 million courses of the drugs have been prescribed in the United States to women unable to conceive (1993 figures).

Pergonal and Metrodin are made from the urine of 100,000 donor women who provide twice daily urines. Aeres-Serono, the parent company, had revenues of $153 million from Pergonal sales in 1994. It is noteworthy that these "urine donor's health must be monitored closely" - yet the recipient of these drugs has no health monitoring. Aeres-Serono, the parent company, intends to have most of its drugs genetically engineered in 1996 (Adelson, 1995).

"It has been hypothesized that reduced uterine receptivity after superovulation for in vitro fertilization may play a significant role in reducing embryo implantation rates." (Rogers et al., 1991, p.583). "The results from this study demonstrate that women being superovulated with CC/hMG develop a significantly thinner endometrium with a significantly reduced glandular volume compared with women receiving buserelin acetate/hMG. ... There are already published studies that show that CC impairs endometrial receptivity in animals... (Ibid, p.586).

There is a multitude of various sera that the embryo is cultured in - from fetal calf serum, to cancer cells, antibiotics, and hormones ... few studies have been done to assess the individual co-culture, never mind the synergistic effect of all the different variants that the egg and/or sperm has been exposed to.

Regarding the risk of ovarian cancer in fertility treatment, the International Federation of Fertility Societies (IFFS) stated during the 1995 International Consensus on Assisted Procreation: "Doctors ... must inform the patients *and keep detailed files for further retrospective studies. "* In the United States, neither the government, research institutions, or drug companies have conducted long term studies on the effects of fertility drugs on the women or their offspring (Herman, 1994), and the long term health impacts of'reprotech' are unknown (Ibid; Costigan, 1993; Napoli, 1994).

In November 1992, the American Journal of Epidemiology published the findings of Stanford epidemiologists' Alice Whittmore review of data from 12 previous studies on ovarian cancer- a three times greater risk of ovarian cancer with fertility drug use was found, and a twenty seven times greater than expected incidence in nulliparas. Despite the small numbers in these studies, the Center for Population Research and National Cancer Institute have called for further research (Spirtas, 1993; NCI, 1993), and Columbia University epidemiologist Carolyn Westhoff argues the findings are "a big enough deal to recommend against egg donation by healthy women to infertile women" (Raloff, 1993). Drug firms were subsequently asked by the Food and Drug Administration to include the risk of ovarian cancer in its product literature.

Steven Kaufman, M.D. of the National Institute of Child Health and Human Development's Contraceptive and Reproductive Evaluation Branch states "... these provocative findings justify an increased level of concern about a possible causal relationship" between the use of fertility drugs and cancer." (Reynolds, 1993).

In September 1994, *a* study by Rossing (the 'Seattle study') concluded "prolonged use of clomiphene may increase the risk of a borderline or invasive ovarian tumor." In this study, the "drug therapy, rather than any preexisting ovulatory abnormality" appeared responsible for the ovarian tumors (Napoli, 1994). Currently, the NICHD is supporting an expansion of the Seattle study, along with further study by the NCI (NCI, 1995) The studies that are currently underway are not open to any woman undergoing fertility treatment, but rather the subjects are recruited - potentially biasing the sample.

Whittemore states the increased use of fertility drugs lends "urgency to the question of their carcinogenic potential... There needs to be long-term, organized follow-up of women who have taken fertility medications, to look at not only morbidity in the women themselves but also birth defects and long-term morbidity in the children of these fertilizations." (Reynolds, 1993). To this end, there has been a "limited American research effort" (Asseal, 1993).

It should be noted that most evaluations of ART infants are performed at or shortly after birth - yet an early landmark study of congenital malformations concluded that "less than one-half (43.5%) of the malformations found among live-born infants were suspected or noted at birth" (Mclntosh et al., 1954).

In Israel, a nationwide case-control study reported to the Israel Cancer Registry between 1990 and 1993 concluded: "that the use of ovulation induction agents, in particular hMG, may increase the risk of epithelia ovarian tumors. ... Since 1982, notification of malignant and related diseases to the Israel Cancer Registry by physicians and hospitals has been compulsory by law." (Shushan et al., 1996, p. 13)

There is no such law in the United States. Without adequate data collection, there cannot be data

analysis to definitively determine the risks of these drugs. Many of the studies that are done involve as few as 6 to 25 patients - while acknowledging that many more patients (in the thousands) would be needed to draw definitive conclusions. These treatments have not been scientifically proven safe or efficacious, and in fact are experimental, and women and their eggs are paying physically and financially to be human guinea pigs. Given that it is research, written informed consent must be guaranteed - yet these women are led to believe they are consumers of sound science and are unaware of their research subject status. With the thrust of genetic engineering taking center stage (with all the latest tests, machines, and probes), it is clear that the goal of reproductive technologies is centered on eugenics, and not 'helping women have children'.

With such a direction, and with no boundaries and the promise of profits, reproductive technologies hold the promise of danger. Ectogenesis also looms large. One researcher has stated: "It may be concluded that in many patients the uterine cavity may not be a favorable environment for early IVF embryos." (Lopata, 1995). [Lopata also states that "... a large number of complex laboratory procedures are performed on embryos that have not revealed their capacity to develop to the blastocyst stage. For example, embryo freezing is almost exclusively being done using very early embryonic stages and large numbers of such embryos do not have the capacity to form blastocytes. Apart from the excess work load, this creates problems of storing numerous embryos not capable of becoming blastocysts." (Ibid, p.4S)].

Regulation may not be a total answer, but some form of control must be applied to this runaway field. The 1992 Fertility Clinic Success Rate and Embryo Lab Certification Act was scheduled to be put into place by 1994 - but has yet to be implemented due to "lack of funding" (despite the law incorporating fees into the language to cover the cost of implementation). This law, when enacted, would require accurate reporting of success rates (5 fertility clinics have been sued by the FTC for inflating their success rates and misleading and deceiving consumers), and would establish a *voluntary* model program for certification of the embryo lab (which states may or may not adopt). No provision within this federal bill, Public Law 103.493, addresses the practices or procedures of the fertility clinic itself, nor is there any provisions for mandating informed consent regarding the risks. In mid November 1995, the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technologies (SART) released a statement on the regulation: "... now is the time to consider establishing an independent licensing authority".

A first in the nation bill to regulate fertility clinics and mandate informed consent of the risks was filed in Boston in 1992 (House 5050) - but remains pending; fertility clinics, fertility doctors, the Boston Fertility Society, and RESOLVE, have opposed this bill. RESOLVE first opposed this bill in March 1993 ... in a June 1993 RESOLVE Newsletter, it notified its members for the first time about the Massachusetts bill. Although RESOLVE promotes itself as the "voice of the infertile", it neither informed nor polled its members regarding this important issue before delivering its position on this bill. Of note is the long history of financial ties that RESOLVE has with the fertility drug companies, especially Serono. According to the Financial Disclosure Forms filed by RESOLVE with the Massachusetts Attorney General's Office, Resolve received $247,930 from Serono in 1995 *alone*.

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