WOMEN AS TEST-SITES FOR FERTILITY DRUGS: CLOMIPHENE CITRATE AND HORMONAL COCKTAILS

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Synopsis—Clomiphene Citrate is a drug which has been given to women for over 20 years for conventional infertility treatment. More recently it has been used on reproductive technology programmes in order to assist in the superovulation of women. It is also being given to women in 'hormonal cocktails' with other drugs. Some doctors contend that clomiphene citrate is safe and has no negative side effects for women. In this analysis of some of the medical and scientific literature on women, we consider research evidence concerning the effects of clomiphene citrate in animals, the birth defect rate for women who have taken the drug, the chromosomal anomalies in eggs produced using clomiphene citrate, and cases of ill health in women, including cancer leading to death. There is evidence that clomiphene citrate may have a long life span in a woman's body, and may cause deleterious effects in the woman's children and in a woman herself because of this. Similarities have also been shown between clomiphene citrate and DES (Diethylstilbestrol) and these are investigated. We also consider the dosage of clomiphene citrate recommended by a pharmaceutical company, and show that women are actually administered doses outside these recommended levels. And finally, we consider the experiences of women themselves with the drug. These show a variety of negative "side effects," including depression and emotional instability, as well as more severe physical adverse reactions. We conclude that the level of risk which medical science feels is acceptable in terms of its experimentation with women concerning these and other drugs, is not acceptable to us. We stress that this is particularly important considering the wide range of women who are now consuming clomiphene citrate, including healthy fertile women who are seeking *in vitro* fertilisation because of their male partner's infertility or subfertility. We recommend that clomiphene citrate not be administered to women and that women become aware of the risks they may be taking when they consume this drug and other 'hormonal cocktails.'

An article published in an Australian newspaper (Rowland, 1987b) suggested that clomiphene citrate, a drug used for conventional infertility treatment and on IVF programmes internationally, is dangerous to women, has severe side effects, may cause cancer and may be similar to DES. In response, Dr. David Healy of the Medical Research Centre at Prince Henry's Hospital in Melbourne, wrote a letter to the paper, not published by them, but since given to journalists as the final word on the matter.[1] It included the following statements:

> *Clomid is not a hormone,* it is a *medicine* which has been used *safely* for more than 20 years for the treatment of infertility, which is speci fically related to non ovulation . . . the side effects which the Dutch and Geelong women claimed were due to treatment by Clomid such as depression, lethargy and impaired vision are *NOT consistent with the side effects doctors would expect during or after the use of this drug* . . . in fact the side effects of Clomid are only minimal and are no more than hot flushes or mild sweats . . . the structure is NOT almost identical to DES. Medical practitioners and pharmacists are aware of this scientific *fact* . . . Lastly, there is no evidence that super-ovulation increases the risk of ovarian cancer. Indeed, women who have had children have less risk of ovarian cancer than childless women. Quite simply, helping infertile women have children decreases, not increases their risk of ovarian cancer . . . *it is concerning and unacceptable that these scientific errors continue to appear in print,* (capitals his, emphasis ours)

We decided to take a closer look at clomiphene

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citrate and to determine where the 'scientific errors' might be appearing in print. The result is an analysis of some research findings on the drug which suggest that statements such as those contained in Healy's letter are ill-informed and misleading. Women who take this drug should assess the information available and make their own assessment of the 'scientific' *facts*.

INTRODUCTION: WHO CONSUMES CLOMIPHENE CITRATE?

Since the birth of the first child conceived by *in vitro* fertilisation (IVF) in 1978, the grief and pain felt by some infertile people about their unmet desire for their own biological child has been transformed into a public commodity called 'the right to have children.' Reproductive medicine and science along with commercial interests have created an international industry and continue to develop a constantly expanding range of new 'treatments' which, supposedly, will cater for this need.

These range from the administration of drugs to induce ovulation in 'conventional' infertility treatments to the invasive and dangerous surgery of IVF—basically a failed technology with some clinics having a zero take-home baby rate and the most 'successful' having a 92 to 95 percent 'failure' rate.[2] IVF itself is an important prerequisite for genetic engineering: it provides the eggs and embryos necessary for experimentation (produced as 'spares' on IVF programmes or from donor women attending for sterilisation) as well as a constant 'supply' of women whose bodies are readily available test material for research (see Rowland, 1987a; Klein, 1987; Bartels, 1988).

One of the central elements of 'fertility' treatment for women is an extensive use of hormonal drugs. A primary drug used is clomiphene citrate, which will be the focus of our paper. Increasingly, however, clomiphene citrate is being given as a 'cocktail' in various combinations with HCG (human chorionic gonadotrophin) and HMG (human meno-pausal gonadotrophin) and sometimes with FSH (follicle stimulating hormone) and LH (luteinising hormone). Increasingly, also, these drugs are used by a much wider range of women, including those who are *not* on reproductive technology programmes, and those who are 'normally' functioning *fertile* women.

Thus, women who are anovulatory (not ovulating) or who have amenorrhoea (not menstruating), are given clomiphene citrate (Laborie, 1988; Cabau, 1986; MIMS 1984, 1987). A regime of superovulation (clomiphene citrate alone or with other drugs) may also be used on women entering artificial insemination by donor programmes who are there because their husbands are infertile. The assumptions behind this procedure are that the production of more than one egg will increase the chances of fertilisation and it is easier to predict the time of ovulation (Lasker and Borg, 1987).

Women using IVF and its many variations are submitted to superovulation too. These women include the infertile woman, on IVF for her own infertility problem, and the donor woman who is donating an egg to another woman who cannot produce eggs herself. Donor women are sometimes relatives, such as in the recently discussed IVF/surrogacy case between sisters in Victoria, Australia, using the egg from an infertile sister and placing it after fertilisation with donor sperm into the womb of the fertile sister who intends to carry the child to term (Peak, 1988). Or donors may be anonymous, for example women undergoing elective tubal ligations (Brozan, 1988). They may also be women who are asked to donate eggs when they are undergoing a hysterectomy (Messinis *et al.,* 1986), and in some instances have been offered a free sterilisation if they donate eggs (Rowland, 1987a). There clearly exists the demand for ovum donors: in one North American IVF clinic, people on the waiting list were given priority if they brought in other women who would provide eggs 'into the pool of donors' (Lasker and Borg, 1987: 96). What needs to be emphasised here is that in these cases of donation, *it is healthy, fertile women who are superovulated.*

Women on surrogate motherhood programmes in North America have been given clomiphene citrate since at least 1983 (Gorney, 1983). And Gena Corea has recently documented two cases of so-called surrogate mothers in North America who were superovulated in order to produce multiple eggs, thus increasing the chances of becoming pregnant after artificial insemination with the buying man's sperm (in Klein, in press). In addition, the technique of micro-injection of a single sperm directly into an egg devised to help

subfertile men, requires the superovulation of their healthy and fertile partners to produce the necessary mature eggs (Pirrie and West, 1988).[3]

Rowland (1987a) has pointed out elsewhere that the move towards embryo experimentation also opens up a new population of women as experimental subjects. Embryo experimentation necessitates the collection of large numbers of eggs, but women on IVF programmes are usually unwilling to give up both their eggs and their 'spare' embryos for experimentation. There is an increasing movement of medical experimentation into the so-called 'normal population,' for example in England and Scotland medical researchers prepare to collect more and more eggs in connection with sterilisation. These women need to be superovulated in order for them to produce enough eggs for the purposes of science before they are sterilised.[4]

Concern about this is borne out by a study by Braude *et al.* (1984) reported in *Fertility and Sterility* of patients awaiting sterilisation who were asked to donate their eggs for the purpose of 'testing the fertilising capacity of spermatozoa from clinically infertile men.' Forty seven percent of these patients agreed to be donors and were superovulated with 100mg or 150mg clomiphene citrate for five days. (A dose outside the regimen recommended by the pharmaceutical company.) Eggs were then collected from these women for the purposes of experimentation. The final collection of eggs for this study was stimulated by HCG.

Given the extensive use of procedures which require the prescription of hormone-like substances for ovulation or superovulation to a constantly growing number of women, it is important to analyse what is known about such drugs. This paper will focus on one of these drugs, clomiphene citrate. After a brief summary of women's reproductive biology we will investigate the nature of the drug: what it is, how it acts, and whether there is a dosage that can be considered 'safe.' We will compare it with other drugs that have a similar chemical structure. We will also look at combinations – or 'hormonal cocktails' as French gynaecologist Anne Cabau calls them – which are administered to women. Evidence from the medical literature as to the 'side effects' in women treated with the hormone-like substances and in their children will be discussed, followed by women's experiences of the drug as we learned about them in our own research from women undergoing both 'conventional' infertility treatment as well as IVF (Klein, 1988a, in press). Contradictions, paradoxes, but above all, an alarming amount of evidence about the potential of the drugs to cause serious health problems will be discussed.

1. WOMEN'S REPRODUCTIVE BIOLOGY

Before dealing with the nature of the drugs, it is useful to recall women's reproductive functions and specifically the process by which a woman's body would normally produce one mature egg per month. It is important to realise, however, that reproductive medicine does not have a definitive understanding of the complex female reproductive system – and spe-cifically, what happens when this system is interfered with through the administration of hormone-like substances. While some models have been established for how the various hormones are controlled and in turn influence one another, the main problem for the scientists is the fact that every woman's body has her own rhythms and cycles which may vary substantially from what is considered the 'clinical norm.' A well-known Australian IVF scientist told a woman on an IVF programme after treatment with Clomid when abnormal, possibly cancer-forming, cells in her cervix were removed (Klein, 1988a):

> Well look, we are considered to be the best in the world and we practically know nothing. You know, next to nothing: we can't tell, we don't know.

Canadian researcher Anne Rochon Ford quotes one American biologist as saying: 'The gynaecologist/obstetrician is probably more of a medical empiricist than any other specialist; that is, the gynaecologist administers hormones as a treatment because they work and not because there is a clearly-defined understanding of their action in the body' (1986: 31).

What follows is a short summary of some of the main mechanisms of a woman's reproductive cycle and how it supposedly functions.

At birth a woman's ovaries contain around 400,000 follicles: balls of cells with immature eggs

at the centre. Only about 300–500 of these will develop into mature eggs to be released one by one (rarely two or three) per month in the lifetime of a woman.

Stimulated by the anterior pituitary gland which produces two hormones which in turn affect the growth of the ovaries (FSH-follicle stimulating hormone and LH-luteinising hormone, both called gonadotrophins) one of the cell layers in one of the follicles secretes estrogen. The follicle, with the maturing egg inside, moves toward the surface of the ovary. Just before it is released from the ovary, this cell layer starts secreting progesterone as well as estrogen. After ovulation, the empty follicle is called the corpeus luteum. If the woman becomes pregnant the corpeus luteum produces progesterone in order to maintain the pregnancy.

When the cell layer in the follicle is secreting estrogen, this also causes the uterine lining (the endometrium) to proliferate, which prepares the uterus to accept the egg. The progesterone secreted by the ruptured follicle after the egg has been released, causes glands in the endometrium to secrete embryo nourishing substances. The fertilised egg will implant only in a lining in which these substances are secreted and not in one where the lining is merely proliferating.[5]

2. CLOMIPHENE CITRATE: THE NATURE OF THE DRUG

Some women do not produce mature eggs and are referred to as anovulatory. Clomiphene citrate is often used to induce ovulation in them, that is to encourage the growth and maturation of follicles/eggs. It has been used internationally for over 20 years since its first prescription in the early 1960s. Clomiphene citrate is best known as Clomid which is the trade name for a form of clomiphene citrate marketed by Merrell Dow Pharmaceuticals. However, Serono also produces it as Serophene.

There is debate throughout the medical literature on how clomiphene citrate actually works. Originally, it was used to *prevent* ovulation. Then it was seen to *induce* ovulation. The MIMS, the book of drugs from which Australian doctors select those to prescribe, contains the Merrell Dow analysis of Clomid which indicated in 1984 that "the exact mechanism of actions in humans is unknown, but it is postulated that Clomid acts by stimulating the output of pituitary gonadotrophins' (MIMS, 1984: 325). By 1987 the description is still tentative: 'The ovulatory response to cyclic Clomid therapy *appears* to be mediated througho increased output of pituitary gonadotrophins . . . ' (MIMS, 1987: 373; our emphasis).

Assuming that this is true, Clomid would seem to act on the hypothalamus and the pituitary gland. The hypothalamus is a gland at the base of the brain which controls the pituitary gland, which in turn determines which hormones are released into the body and thereby control a woman's menstrual cycle. One theory is that clomiphene citrate is interpreted by the body as an anti-estrogen. It tricks the pituitary into producing FSH and LH. FSH is a hormone which controls the growth of the ovarian follicle and the maturation of eggs in a woman. LH is a hormone which controls the release of the mature egg from a follicle and then supports the development of the corpus luteum in a woman (Dettmann and Saunders, 1987). If Clomid thus tricks the pituitary into producing these two hormones, they stimulate the ovary to ripen and release one or many eggs.

Yee and Vargyas (1986: 134) point out in their historical summary of the use of clomiphene citrate, that it needs to be given early enough in the cycle of a woman to override the 'mechanisms which allow for dominant follicle selection to occur.' It overrides the normal process through which the 'dominant' and ripening follicle *alone* is released from the ovaries. So clomiphene citrate is used to encourage multiple follicle development. This is one of the reasons why women using the drug may end up with multiple births.

Yee and Vargyas write that a problem with clomiphene is that after multiple egg production, the rate of implantation of fertilised eggs is very low. They suggest that it may be that the drug produces detrimental effects in the follicle when the egg is released, thus leading to a corpus luteum which is inadequate or to an unreceptive environment in the endometrium of the woman's womb. This might explain why approximately 95 percent of the embryo transfers do not succeed (Miller, 1988). (But see also section 4.3 on chromosomal abnormalities in the egg cells.)

Scientists seem uncertain about whether the drug acts as an estrogen or as an anti-estrogen, or both. In 1980, Clark and McCormack established that although Clomid acts as an anti-estrogen in some tissues, it also acts as a long lasting estrogen

in other tissues in the body. As Gorwill *et al.* put it (1982: 529):

> . . . clomiphene citrate ... is a mixture of two isomers of a compound that has a structural similarity to diethylstilbestrol. The biologic effect of clomiphene citrate depends upon *the system* in which it is studied. Both estrogenic and anti-estrogenic effects are seen, (our emphasis)

Gorwill *et al.* indicate here that clomiphene citrate also has a structural similarity to diethylstilbestrol (DES). More recent research has confirmed the close relationship between DES and clomiphene (Direcks and Holmes, 1986; Cunha *et al.,* 1987). The structural similarities between the two drugs may have serious implications for the use of clomiphene. DES was a drug administered internationally to between 4 and 6 million pregnant women from the 1940s to the early 1970s to supposedly stop miscarriage (Driscoll and Taylor, 1980). Some of the women who were given this drug were used as experimental subjects and were told that they were taking a vitamin tablet. There was a time bomb effect with DES and years later daughters of these mothers are now suffering cancers of the vagina and cervix at a rate higher than that of the female population of their own age. They also experience increased rates of infertility, spontaneous abortion, ectopic pregnancies and premature deliveries. Sterility problems have also been detected in some sons of DES mothers. More than 30 years after they had used the drug, the women who took DES are also suffering from 40 to 50 percent higher rates of breast cancer than women of their own age (Corea, 1985a; Direcks and Holmes, 1986; Scully, 1980; Driscoll and Taylor, 1980). It is outrageous that despite these proven adverse affects, DES continues to be sold in so-called Third World countries (Direcks and 't Hoen, 1986).

Gerald Cunha and his colleagues in California looked at the differences between DES, clomiphene and tamoxifen (an anti-estrogen used to treat breast cancer) in the developing human female genital tract (Cunha *et al.*, 1987). The study was conducted on 54 fetal reproductive tracts taken from 54 aborted human fetuses. The genital tracts of these 4–19 week old fetuses were grown for 1–2 months in host mice. There were four groups of mice involved: a group of controls who were untreated, a group who were given clomiphene, one given tamoxifen and another given DES. The specimens of human reproductive tracts were grown to the equivalent of 15 weeks. The mice were implanted with large doses of clomiphene and DES (20 mg pellets). Merrell Dow Pharmaceuticals argued that the doses used were not comparable to the doses of clomiphene supposedly given to women (Rodell, 1988). Nevertheless, Cunha *et al.* found that 'clomiphene and tamoxifen elicit changes in the human fetal vagina comparable with those of DES' (1987: 1137). During the study, the fallopian tube was also affected by clomiphene. The authors point out that the results 'emphasised the heretofore unrecognised estrogenicity and potential teratogenicity of triphenylethylene anti-estrogens on the developing human genital tract' (p. 1132). They conclude that:

> On the basis of the data presented here, anti-estrogenic triphenylethylene compounds are potent estrogens in the human fetal genital tract and have the distinct potential for eliciting teratogenic change (p. 1142).

The MIMS lists an astonishing array of possible negative effects of Clomid. The entry 'adverse reactions' begins with the following sentence:

> Side effects are not prominent and do not interfere with treatment when the recommended dosage of Clomid is given (1984: 325; 1987: 373).

Yet, it then continues with an *alarming* list of side effects which it indicates become more frequent and severe the higher the dose and the longer the course of Clomid.

> The more common side effects are hot flushes, abdominal discomfort (distension, bloating, pain or soreness), ovarian enlargement and visual blurring . . . other less frequently reported symptoms included nausea or vomiting, increased nervous tension, depression, fatigue, dizziness and lightheadedness, insomnia, headaches, breast soreness, heavier menses, intermenstrual spotting, weight gain, urticaria and allergic dermatitis, increased urinary frequency and moderate reversible hair loss (1984: 373).

In 1987, they added abdominal symptoms related to 'ovarian enlargement' and:

> Rare instances of massive ovarian enlargement and rupture of a lutein cyst with haemoperitoneum have been reported. Visual symptoms, described usually as 'blurring' or spots and flashes (scintillating scotomata), increase in incidence with increasing total dose and disappear within a few days or weeks after Clomid is discontinued (1987: 373).

Patients 'should be advised' that there may be the possibility of visual symptoms and that administration of the drug should stop should this occur because '*the significance of these symptoms is not yet understood*' (1987: 373; our emphasis).

The term 'side effects' seems a highly inappropriate description for such debilitating adverse reactions as ruptured cysts which necessitate emergency surgery, and potential serious health hazards such as interference with 'cholesterol synthesis' after prolonged use (p. 326).

The MIMS also indicates that there have been some birth defects reported. In 58 children from 2,369 delivered pregnancies from mothers treated with clomiphene, 4 of the children were stillborn, 14 were from multiple pregnancies and the remaining were from single births, including abnormalities such as Down's syndrome (5), congenital heart lesions (8), microcephaly (2) and a variety of other problems. Eight of the 58 children born were those whose mothers had inadvertently taken clomiphene during the first six weeks after conception (1984, 1987).

In sum, a long and disturbing list of indications, precautions and adverse reactions are listed in the MIMS for Clomid, a drug that 'some doctors are handing out like candies' (Direcks, personal communication to Klein, February 1988). And this information is at the fingertips of every doctor who prescribes the drug. We therefore must ask whether doctors tell the women about the risks they take when they start on a course of Clomid. But most importantly, *is a drug which can lead to such serious adverse reactions and has so many potential problems safe enough to be administered to any woman?*

As we will point out in section 4 there is substantial scientific evidence in the medical literature concerning the dangers associated with clomiphene citrate. But when reading this literature, it is disturbing to notice that researchers continue to assure their readers that despite their discussion of a long list of serious health risks associated with the drug, there is nothing really wrong with it.

How serious must side effects be which would indeed be acknowledged as 'interfering with treatment?' This is a continuing problem in the administration of drugs, spelt out particularly clearly in the long standing historical relationship between medicine and women (Ehrenreich and English, 1978; Corea, 1985a). Indeed, there seems to be a peculiar reluctance involved in assessing negative affects of drugs on women.

3. HORMONE COCKTAILS

Yee and Vargyas (1986) note, however, that clomiphene is not producing *enough* eggs in women, particularly for the purposes of IVF. So it is now often used in association with other drugs. Human menopausal gonadotrophin (HMG) is one of the other drugs administered to stimulate the development of multiple follicles and therefore multiple eggs. It is a menotrophin, a purified preparation of gonadotrophins which is extracted from the urine of post menopausal women. HMG is usually administered to women in Australia as Pergonal. Pergonal works directly on the ovaries and is usually injected rather than taken orally. However, although Pergonal may make the ovaries ready to produce a number of eggs, women are usually administered a further stimulant, human chorionic gonadotrophin (HCG), often marketed as Pregnyl, to stimulate the release of the eggs. HCG also promotes the implantation of the embryo as it is the hormone produced by the developing embryo and later by the placenta. But when administered artificially, it is used to 'induce ovulation at a precise time' on IVF and GIFT programmes (Dettmann and Saunders, 1987: 214; Pfeffer and Woollett, 1983).

French gynaecologist Dr. Anne Cabau is concerned about the dangers involved in using these combinations. She points out that in the last ten years, we are witnessing 'abusive indications' of 'the strangest mixtures' of drugs (1986: 2–3). She warns against such 'explosive cocktails,' noting as particularly dangerous the combination of clomiphene citrate, HMG and HCG, as well as

HMG and HCG together. She points out that until ten years ago clomiphene was prescribed to anovulatory women and HMG to women with amenorrhoea caused by a hypothalamus/pituitary malfunction. But today they are prescribed together to 'women with insufficient mucus production, women with dysovulation, irregular menstrual cycles (particularly with regard to inseminations), repeated miscarriages, altered tubes and women with husbands with a sperm problem' (p. 2). To this, she says: 'We have to add unexplained infertility, women in a hurry and doctors pressed for time' (p. 2). It is not surprising, Cabau says, that increasingly, we see not only multiple pregnancies, but hyperstimulated ovaries which endanger women's lives.

Yet, figures quoted in the official Australian statistics on IVF from 15 units in Australia and 1 in New Zealand indicate that the 'explosive cocktail' of clomiphene citrate, HMG and HCG was administered to 58 percent of clients from 1979 to 1985 and 72 percent of women in 1986, a substantial increase. Clomiphene citrate and HCG were administered to 10 percent of women in 1979–1985 and only 0.8 percent in 1986. Figures for clomiphene and HMG were 19 percent and 22 percent respectively. No women were reported as receiving *only* clomiphene citrate.[6] In our Australian IVF study only 7 out of 40 women were *not* given clomiphene before egg collection. These 7 either could not remember the name of the drug they were given (5) or listed other drugs (2).

Because of space limitations, this paper will focus on the research concerning, and the application of, clomiphene citrate. But it is important to remember that it is usually administered in a regimen with other drugs. The inter-relationship between them appears not to have been explored in detail within the medical literature which is one cause for concern.

4. SCIENTIFIC RESEARCH ON CLOMIPHENE CITRATE

4.1 Animal studies

A considerable number of studies have investigated the effects of clomiphene on animal offspring. For example, in 1966, New-berne, Kuhn and Elsea published a study on the toxic effects of clomiphene, stressing that it was a drug which had exhibited both estrogenic and anti-estrogenic activities in immature female mice. Their study investigated clomiphene administration to rats and dogs which resulted in significant changes in the reproductive system of these animals. Notably, the ovaries of the dogs became atrophied, similar to the atrophic ovaries in the study by Clark and McCormack (1977) of adult rats administered Clomid. They found tumors of the uterus in adult rats who had been given Clomid at the neo-natal stage. They comment that the doses of Clomid they administered were high but conclude that 'although intermediate and lower doses have not been completely evaluated, our results indicate that 10 to 50 percent of the animals will be adversely affected' (p. 165). The same authors point out in a further study in 1980 that at that point Clomid had been 'widely used for the past 15 years to induce ovulation in anovulatory women'. They comment (1980:51):

> This treatment regimen is often continued for many months thus the exposure of women to Clomid can be extensive. Under these circumstances, Clomid may be stimulating some cell types while acting as an antagonist in others. The eventual effects of such stimulation may remain unknown for many years.

They emphasize that Clomid 'could cause hyperestrogenization of certain cell types in humans' (p. 51), and 'may be potentially dangerous for human use' (p. 47).

In a further study on the mouse's vagina which Gorwill, Steele and Sarda indicate 'has been identified as a good developmental model of the human' (1982: 529), both DES and clomiphene were administered to neonatal mice. The results were adenosis in the vagina which can lead, but does not necessarily do so, to cancer. Their primary concern was with the possibility of clomiphene being administered to women who were pregnant. Noting the estrogenic and anti-estrogenic effects of the drug, they comment: 'if clomiphene citrate, given to the human prior to pregnancy to induce ovulation or by inadvertence during pregnancy, were to circulate into the critical time of vaginal differentiation, a similar biologic potential may exist', that is the development of tumors (1982: 529).

Animal studies in general indicate problems with the administration of clomiphene, though

often the dosage administered is considerably higher than the equivalent used in women. Also, there is the problem about the generalisability of animal studies to humans. For these reasons we do not wish to stress them here. Nevertheless, it is important to know that these studies have been conducted since at least 1966 when clomiphene was first administered to women, though researchers primarily stress the impact of the drug on offspring.

4.2 Abnormalities in children born after clomiphene-induced pregnancies

As indicated above (Section 2) the MIMS lists evidence of birth defects in children born to mothers who used Clomid. Evidence in the medical literature continues to indicate that there may be a link between clomiphene and abnormalities in children. In the *Lancet* in 1981, Ford and Little note that although research studies mention that a serious consequence of clomiphene therapy is ovarian enlargement in the mother, they have also seen a case of ovarian enlargement in the fetus. They record the case of a baby born with a large ovarian cyst to a mother who had been taking 'clomiphene *immediately before* conception' (our emphasis). They comment that 'while the association of fetal abnormalities and clomiphene is by no means proven, clomiphene is excreted slowly and *may still be present six weeks after its administration'* (p. 117; our emphasis). So clomiphene may pass through the placenta into the developing fetus.

A further study by Laing *et al.* (1981: 1107) published in the same issue of the *Lancet* describes a case of a baby whose mother received clomiphene for three months in order to become pregnant. Her dose was the lower regimen of 50 mg daily for 5 days. They note that 'the pregnancy, delivery and routine examination at birth were normal but at the age of 5 months the baby was referred because of parental concern about his vision' (p. 1107). On testing, the child had a vision defect (retinal aplasia). The researchers comment that in one survey of 2,616 women treated with clomiphene, 2 percent of the children had visual symptoms. They note further studies in both animals and humans where visual defects appear to be occurring. The problem with the child they were dealing with appeared to be similar to the kinds of problems recorded in mothers on clomiphene. Like Ford and Little (1981) they warn that clomiphene might remain in the woman's body long past the time of conception. However, in spite of this disturbing data, Laing *et al.* (1981) comment: 'despite the evidence for a direct toxic effect on the maternal retina and the long half-life of closely related compounds, it seems unlikely that clomiphene could have a direct effect on the embryonic eye' (p. 1108). Again, as with many other studies recording damage to either mother or child, researchers come up with the conclusion that ultimately no conclusive evidence against the drug is to be found.

A further area of concern is anencephaly and clomiphene. In 1973 among others (e.g., James, Barrett and Hakim, 1973; Guibaud *et al.,* 1973) Dyson and Kohler (1973) noted that: 'Drugs that stimulate ovulation have not been included in the list of possible or probable aetiological factors of anencephaly; the only abnormality with which they have been associated is multiple pregnancy' (p. 1256–57). They go on to record two cases in which women delivered anencephalic babies after a treatment of clomiphene. In one instance the woman was given 50 mg daily for five days on two occasions and 100 mg for five days on three occasions. In the second case the woman was given 50 mg daily for five days over five months. The researchers conclude (p. 1256–7):

> that the possibility of a causal relationship between ovulation-stimulating treatment and C.N.S. [Central Nervous System] abnormality should not be dismissed lightly. If additional evidence is found for this hypothesis the question arises whether, in case 1, the ovum was damaged before implantation or even before fertilisation.

This report prompted Sandier (1973) to report a further case of anencephaly after clomiphene stimulation, when 'the patient must have been under its influence when conception took place' (p. 379). But because the manufacturers in America 'have no evidence that clomiphene produces anencephaly of this type,' he concludes that 'it may not be the clomiphene but ageing of the ovum which may be a factor.' The woman was *25 years ofagel*

In another study in 1978, researchers recorded two further cases. Biale *et al.* say that: 'Further

sporadic case reports of anencephaly occurring with ovulation stimulation by clomiphene have appeared more recently' (1978: 483). They also note the increased frequency of chromosomal abnormalities in abortions after induced ovulation and discuss the continuing medical explanation for these problems: that the underlying sub-fertility of the *women* for which the drug was administered was the problem, rather than the drug itself. We will discuss this explanation for abnormalities later. However, Biale *et al.* conclude (p. 484):

> On reviewing the literature we consider that the possibility of a causal relationship between ovulation stimulating treatment and central nervous system abnormalities should not be dismissed lightly, but much additional evidence will be needed to establish the hypothesis.

We can assume that they mean that the continuing administration of the drug to women will lead to more and more data on abnormalities in children which will then allow true statistical comparison to be done!

In 1983, a Japanese study by Kurachi *et al.*, prompted by the concern over the possible teratogenicity of clomiphene treatment for the children born, led researchers to assess the pregnancy rates of women using clomiphene in Japanese hospitals. They looked at all pregnancies from women so treated over a five year period from 1976 to 1980. They found a 2.3 percent abnormality rate in infants. They commented that this rate of malformation was not significantly different from a group of spontaneously ovulating women – 1.7 percent – and infer that there is no cause for worry. A further study of its kind, assessing birth rates in Swedish hospitals, came to similar conclusions. Looking at the incidence of malformation in the period 1967 to 1974, Ahlgren, Kallen and Rannevak conclude (1976: 374):

> A slightly increased incidence of severely malformed infants was found in pregnancies occurring after clomiphene treatment. This might indicate a direct teratogenic drug effect, but it could equally be an expression of the sub-fertility which made the therapy necessary as has been repeatedly suggested in the literature.

As with a number of other medical studies (some of which we have already referred to earlier), the researchers then go on to suggest more monitoring and screening in order to stop women from producing malformed infants. They too stop short of saying that clomiphene itself may be the problem.

Yet Dr. Paul Lancaster of the Perinatal Statistics Unit in Sydney, Australia does see cause for concern in similar statistics in Australia. Data from the Perinatal Statistics Unit up until and including 1987 indicate that the rate of major congenital malformation in children born was 2.2 percent. This compares unfavourably with the incidence of 1.5 percent for major malformations in Australia. Some caution must be used in comparing these results, however, because the IVF figures do include terminations of pregnancies at an early period which may not have been included in the general population statistics. Nevertheless, these figures caused Dr. Paul Lancaster (1987) to write to the *Lancet* about his concern over these rates of malformation. The major malformations at this stage are spina bifida and transposition of the great vessels of the heart. In addition, the perinatal death rate was twice the number expected compared to general population statistics.[7]

There was also a very high rate of premature deliveries: 26.9 percent. This is worrisome when studies of low birth weight babies show that at 2 years of age, 'despite better intensive care techniques, they are still significantly more physically and mentally impaired than normal infants.' Dr. Neville Newman has said that even though the technical skills will keep low birth weight babies alive 'this is merely the beginning of what may prove to be a long and arduous life of disability,' having a disturbing influence on the functioning of families (Robinson, 1986). This is an important point which could prove tragically true in the years to come.[8]

Though the medical profession argues that IVF may be the way to healthier children for those with a genetic problem or other kinds of continuing 'abnormalities' (e.g., sperm with low motility), these findings are a contradiction in terms. One might expect that with all the technology and the constant screening of embryos which take place on IVF programmes, there would in fact be a *lower* rate of birth defects. That *new* problems seem to be created needs serious thought and attention in the discussion of whether IVF – and the drugs associated with it – are safe for women and their

children.

Discussion about the possibility of a long life span of clomiphene continually recurs within the medical literature. If the drug is still present in the woman's body while the embryo/fetus develops, damage could be done, for example, to the developing reproductive tract. This raises the question about long-term effects after clomiphene administration.

No entry exists with regard to the *life span* of Clomid in the MIMS, though there are intimations about its potential to remain in the woman's body past conception and hence, in the case of a pregnancy, its possible contact with the developing embryo whether conceived *in vitro* or 'naturally.' They say:

> Although there is no evidence of a 'carry over effect' of Clomid, persistent spontaneous ovulatory menses have been noted after Clomid therapy in some patients (1987: 373).

Merrell Dow do recommend, however, that Clomid should not be used during pregnancy. They indicate:

> Although *there is no evidence that Clomid has a harmful effect on the human fetus,* Clomid does damage rat and rabbit fetuses when given in high doses to the pregnant animal (1987: 373) (our emphasis).

The first part of this statement seems in clear contradiction to the evidence of birth defects in children whose mothers took Clomid when pregnant, cited in the MIMS description itself. The statements about the issue of the life span of the drug as well as its effect on the human fetus raise the question of what pharmaceutical companies count as 'evidence.'

Noting the similarity between Clomid and DES, Canadian infertility specialist Hugh Gorwill comments on the possible effects on children as they reach maturity. In an interview in 1984 he said: 'It raises the concern that potentially, Clomid-exposed daughters could be at risk for adenosis . . . which may have the effect on the [vaginal] tissue that somehow leads ultimately to cancer.' In other words, he is worried about the risk of fetal contact with Clomid. In her interview with Gorwill, Canadian journalist Dorothy Lipovenko notes that Clomid can remain in the body for up to six weeks before it is excreted. And, she says, because it is taken 9 or 10 days before ovulation, Clomid can still be around in the early weeks of pregnancy (Lipovenko, 1984).

Both Ford and Little (1981) and Cunha and his colleagues (1987) have expressed similar concern. The latter say: 'Because of the long half-life of clomiphene in the patient, particularly those given large doses during the first half of the cycle, residues may not be cleared soon enough to prevent untoward effects on the developing fetus conceived as a result of prior "anti-estrogen therapy'" (p. 1142).

A further study by Lunenfeld in Israel (1987) confirms these worrisome facts about clomiphene citrate and other drugs such as HCG and HMG. Quoted in *Ob/Gyn News* (April 1–14, 22(7): 6) Lunenfeld said: These drugs have been widely used, but post marketing surveillance on their long-term effect on offspring has not been reported.' Again, concern is expressed about clomiphene in the light of its structural resemblance to DES, which has been linked to 'uterine, cervical and vaginal anomalies.' (Lunenfeld seems unconcerned about potential effects of the drug on the mothers.) He is quoted as commenting (p. 6):

> There has been no evidence that the daughters of women who took clomiphene during pregnancy are at risk of reproductive difficulties, but relatively few such women have reached adulthood since the drug became available, and conclusions must be delayed until an extensive post-pubertal survey can be performed.

Again it appears that the procedure envisaged by the medical profession is to continue administering clomiphene citrate until the numbers of acknowledged long-term anomalies reach 'statistically significant' proportions. Then they might voice serious concern. The intention seems to be to wait until the daughters of mothers who were given clomiphene reach puberty to find out whether they have reproductive difficulties or, in fact, increased rates of cancer similar to the effects caused by DES.

4.3 Chromosomal abnormalities in egg cells

A further cluster of recent studies has drawn attention to the possible detrimental effects of clomiphene on developing egg cells. Due to the

increasing number of IVF programmes which provide researchers with access to 'raw materials' such as unfertilised eggs, recent research highlights chromosomal abnormalities in human egg cells produced in IVF programmes. In 1986, a French research team (Plachot *et al.,* 1986) reported an overall rate of 22 percent of chromosome anomalies. They suggested that (1986: 547):

> This high rate of chromosome anomalies can be explained by the nature of this *population of fertilisation failure,* the frequently advanced maternal age and *the use of superovulation treatments* (our emphasis)[9]

Plachot *et al.* refer to earlier studies by Swedish researchers, Wramsby and Liedholm (1984) and a German research team Spielman *et al.* (1985) who also found chromosomal anomalies in egg cells 'harvested' in an IVF programme. In 1986, Martin *et al.* produced data on abnormal egg cells obtained from women in an *in vitro* fertilisation programme in Canada. And in 1987, Wramsby *et al.,* in a further study, found that infertile women undergoing clomiphene therapy may produce eggs of which as many as half have abnormal chromosomes. Instead of 23 chromosomes characteristic for human beings, these egg cells have between 5 and 25. Wramsby *et al.* suggest that this may be the reason for the low success rate (high failure rate) of embryo transfers in the IVF procedure because the egg cells were already too damaged to develop further.

Discussing this article, a group of Israeli and U.S. scientists (Oelsner *et al.,* 1987) comment on the Swedish group's findings and report 'a direct relationship between the rate of degeneration of blastocysts and concentration of clomiphene' (p. 318). Concentrations of clomiphene in this study were found within the follicular fluid in mice given clomiphene treatment. The researchers hypothesize that this may have been the problem with the women's oocytes in the Wramsby study.

North American infertility expert Georgiana Jaciello called Wramsby *et al.*'s findings 'worrisome' (1987: 318). Nevertheless, despite her expressed concern she goes on to say (p. 318):

> It would seem prudent to view studies of human oocyte chromosome complements with extreme caution in order to avoid sending a message of alarm about abnormalities that might occur in progeny after in vitro fertilisation or other treatments.

Interestingly, doctors seem concerned that this information could be available to the general public including women who might then reconsider undergoing IVF or 'conventional' infertility treatment once they knew about the many possible risks associated with the procedure.

And again, in those cases where an explanation is tentatively undertaken, rather than naming clomiphene citrate and other superovulation drugs as possibly responsible for anomalies, it is the *women* on IVF programmes who are cited as the problem. Martin *et al.* comment (1986: 677):

> In all material obtained from in vitro fertilisation studies, there is a possibility that the frequency of chromosomal abnormalities is inflated since the mean maternal age is elevated and oocytes that are not reimplanted (and therefore available for study) may be morphologically inferior and more likely to have chromosomal abnormalities.

Field and Kerr associate neural-tube closure 'with ageing of the ovum' (1974: 1511) and Plachot *et al.* concur that the problem is 'advanced maternal age' (1986: 548). Blaming women rather than the IVF procedure and the drugs associated with it, also surfaced in a recent Australian debate on birth defects in children conceived by IVF. Asked to comment on the disturbing statistic on birth defects on Australian IVF programmes, Dr. John Yovich, President of the Fertility Society of Australia and head of an IVF programme in Perth, said that the problem could arise with laboratory techniques, but that '*it was more likely to be a factor in the women themselves'* (Mclntosh, 1988; our emphasis).

The renewed discussion of birth defects and later developing anomalies in children born from IVF is disturbing both in the light of these recent chromosomal studies and earlier papers on abnormalities reported in children born after conventional fertility treatment. Any proven links between the drug regimen and abnormalities in children would concern a very large group of women and children: not only those who have undergone IVF but also the much larger numbers

of women undergoing *conventional* infertility treatment.

4.4 Cancer and other health hazards in women

Although the medical research literature seems primarily concerned with results of the drug in children and fetuses, there are some studies which investigate the effects of clomiphene on women themselves. Some of the effects are well known and acknowledged: the possibility of multiple births and of hyperstimulation of the ovaries. Hyperstimulation can lead to a dangerous swelling of the ovaries and/or production of cysts (Ford and Little, 1981: 1107). The formation of cysts can in turn lead to infertility. Canadian researcher Ann Pappert (1988) reports a case from Canada where superovulation treatment on an IVF programme led to a burst cyst (1 of 3) which permanently blocked the woman's one functioning fallopian tube thus rendering her in effect physiologically infertile.

An article in the *Medical Journal of Australia* (Kovacs *et al.*, 1984) indicates other potential problems: the body's defence mechanism against superovulation is overriden, and there may be maternal risks associated with ovarian hyperstimulation, such as 'Meigs-like' syndrome and thrombosis, though the authors feel those risks are unlikely to occur frequently. The higher rate of multiple births causes concern as does an unexpected low pregnancy rate and a higher incidence of ectopic pregnancies (Birkenfeld *et al.,* 1984). Henriet *et al.* (1984) comment that: 'Superovulation is not a simple multiplication of a normal ovulation' (p. 114).

Reported in *Ob/Gyn News* (July 15, 1987; 22(12): 9) at the Fifth World Congress on In Vitro Fertilization and Embryo Transfer in 1987, North American IVF specialist Dr. Karow indicated that hyperstimulation syndrome is a serious complication of ovulation induction with clomiphene, but also with HMG and HCG. Discussing the case of a 33 year old woman who developed ovarian hyperstimulation, he then suggested that a further drug Danazol should be used in order to control hyperstimulation. The intention of this additional drug is to suppress progesterone synthesis and prevent the progression of ovarian follicular growth. Little discussion has taken place so far on the effects of *this* drug. But a general trend can be detected here: the introduction of a *new* drug to solve problems with the old, instead of rethinking the whole concept of administering drugs which cause serious health risks.

There have also been a number of reported cases of severe and rapidly growing cancer after the administration of clomiphene. In one report from Queensland, Bolton discusses two cases where women took clomiphene for infertility (1977: 1776). One woman who was 28 years old, had to abort the fetus after three months and lost both breasts due to cancer. Five years after being administered clomiphene she died of cancer. In a second case, a 29 year old woman had two children a couple of years apart after being treated with clomiphene. She lost her right breast five years after the administration of the drug. Bolton comments: 'clomiphene stimulates ovulation in certain anovulatory women, possibly by triggering the output of pituitary gonadatrophins. The ovaries are thereby stimulated and abnormal ovarian enlargement can ensue. This happened in case 1. Other, less common, side effects include breast soreness and congenital abnormalities' (p. 1776).

The cases of the two women are very worrying. If it was indeed the drug which caused the cancer then clomiphene had a long-term effect on the women. This would be similar to the situation with DES where 40 to 50 percent more breast cancer has occurred in women exposed to DES, 20 to 39 years after they took the drug (Direcks and Holmes, 1986).

A more recent case reported from Bristol in England (Carter and Joyce, 1987), also indicated rapidly growing cancer in a woman on an IVF programme who had been administered clomiphene followed by HMG and HCG: the 'cocktail' Cabau warns against. The woman developed multiple cysts in both ovaries and a tumor was found to fill the pelvis. The cancer involved both ovaries and the tumor covered the uterus and bladder. Loops of the small bowel and the appendix were adhered to the mass. After massive surgery (a subtotal hysterectomy), bilateral salpingooophorectomy and chemotherapy, at the point of writing the paper the authors commented that the woman was said to 'remain well.' They conclude: 'Although hormones may not directly initiate tumor formation, they can act as promoters in the process of carcinogenesis' (p. 127). They then review further studies that suggest 'that elevated gonadotropin levels are implicated in

the development of ovarian tumors' (p. 127). One hypothesis is that 'incessant ovulation increases the risk by not allowing the ovarian surface epithelium to have nonovulatory rest periods and epithelial inclusions created at the site of ovulation might be the source of neoplastic cells' (p. 127).

Carter and Joyce also quote two previous cases which reported ovarian cancer following ovulation induction. They note that: 'It is a matter of concern that in all three cases, the tumors developed with remarkable rapidity' (1987: 128). Yet they still maintain that because of the 'rarity of cases reported despite the widespread use of clomiphene, Pergonal and HCG it [is] unlikely that gonadotropin therapy directly initiates neoplastic growth' (p. 127).

In their analysis of the causes of ovarian cancer, Cramer and Welch (1983) indicate that one cause may be 'a consequence of trauma to the surface of the ovaries caused by "incessant ovulation".' They point out that experimental techniques with high doses of gonadotrophin have been associated with ovarian tumors in animals. They indicate that although the factors leading to both cyst formation and cancer are not fully understood, ovulation has been seen as a major mechanism by which cysts are developed during adult life. Professor Eylard Hall has indicated his concern that there may be 'a possible increased risk of ovarian carcinoma after repeated hyperstimulation of the ovaries combined with multiple follicle-punctures,' though he points out that these suppositions are of a hypothetical nature. His argument is that 'as there is some epidemiological evidence that the use of oral contraceptives reduces the risk of ovarian cancer, it might be that the disease is in some way related to the occurrence of ovulation.'[10] Following this evidence one could fear that repeated multiple ovulation and follicle-punctures might increase the risk of ovarian cancer. Hall points out that these remarks are only meant as a warning and a need to follow women closely who have been given these drugs.

It is evident that clomiphene citrate – administered alone or in combination with other hormones – has stirred a considerable amount of debate in the scientific literature. Clusters of papers around its nature and functioning appeared in the late 1960s and discussions about birth defects, and particularly anencephaly in the early 1970s. From the late 1970s onwards, there appears to be an increasing number of papers pointing to the promotion of cancer in the women who were given hormone therapy. In addition, Gorwill's studies (1980, 1982) and Cunha *et al.*'s findings (1987) focus attention on similarities between DES and clomiphene, and intimate serious concern about long-term effects in the women who take the drug and in their children.

4.5 Summary of the scientific findings

We have shown here a disturbing amount of data on the following: abnormalities and other physical problems in children from clomiphene induced pregnancies; multiple births, which are *not* unproblematic; possible detrimental chromosomal abnormalities in the eggs produced by clomiphene induction; hyperstimulation of the ovaries; and cancerous growth in women taking clomiphene citrate, sometimes resulting in death.

The literature also shows that there is a debate about whether the drug will act as an estrogen or anti-estrogen in individual women. There is uncertainty about its specific action and researchers cannot discern why the drug negatively effects some women and not others.

One manufacturer, Merrell Dow, stipulates that Clomid should not be administered to pregnant women. Yet there is evidence that once administered, clomiphene can stay in the woman's body for six weeks. If a woman is given it between day 5 and 10 of her cycle and if embryo transfer is successful on IVF, or if she becomes pregnant quickly with conventional infertility treatment, the embryo/fetus may be affected. In addition, women are given 'cocktails' of clomiphene citrate, HCG and HMG in varying regimens. The interactions between these drugs and their effects remain unclear and of great concern.

5. WOMEN'S EXPERIENCES

It has been astonishing to learn of this long list of potential detrimental effects ranging from death to severe malformation in both women and children. The least one would expect is that warnings are handed out to any woman before she agrees to the administration of fertility drugs, specifically, clomiphene citrate. One might also expect strict adherence to the dosages recommended by the drug manufacturer.

We have already mentioned the breadth of the

application of clomiphene citrate in terms of the growing numbers of women from very different groups who are exposed to it (see Introduction). The international scientific literature itself indicates the scope of this use. Women writing of conventional infertility treatment discuss its use in Israel, Canada, Australia, England, West Germany, Holland and Austria (in Klein, in press). Women on IVF programmes have spoken of its use in Australia; West Germany (Winkler, in press); Canada (Pappert, 1988; Kozo-lanka, in press); North America (Corea, 1985b); Israel (Goldman, in press); and France (Cabau, 1986; Laborie, 1988), to name but a few of the countries.

It can thus be taken as established that the majority of women internationally seeking treatment for infertility, whether it be by conventional treatment or through using the new technologies, will be prescribed clomiphene citrate at some point in their medical history. In addition, as indicated here and in our introduction, many 'normally' functioning fertile women will also be given the drug.

5.1 Dosage indicated as acceptable compared with dosages administered to women

In this section we will consider the dosages of clomiphene which are recommended and those which are administered to women; whether warnings are given; the experiences of women taking the drug; and how their observations are treated by their doctors. This analysis is supported by our data from a survey of 40 women who left IVF programmes without a child in Australia (Klein, 1988a,b; in press); personal communications from women through our involvement in a national and international network of women concerned about the effects of reproductive technologies; articles by women with a fertility problem for a forthcoming book (Klein, in press); and statements by women in the literature.

Recommendations from Merrell Dow with respect to dosage in the MIMS (1984: 325–26) are that women should be given 50 mg daily for 5 days as the recommended dosage (Clomid is sold in 50 mg tablet form). They point out that doctors need to balance the dose against the potential side effects of the drug (1987: 373):

> Side effects are dose related, being more frequent and more severe when higher doses of Clomid are administered.

The tablets should be continued for 5 days and started on or about the fifth day of a woman's menstrual cycle. If ovulation, but not pregnancy occurs, 'subsequent courses for a total maximum of six cycles of Clomid treatment may be administered' (1987: 373). They add that if one course of therapy for 5 days at 50 mg does not induce ovulation, then a second course of 100 mg per day for 5 days could be given. However, in 1984 they warned:

> Increasing the dosage or duration of therapy beyond 100/mg day for 5 days is not recommended at this time. The majority of properly selected patients will ovulate in response to the first course of therapy, and three courses should constitute an adequate therapeutic trial. If ovulatory menses do not occur after three courses the diagnosis should be re-evaluated. *Treatment beyond this is not recommended in a patient who does not appear to ovulate.* (our emphasis)

Yet by 1987, the dosage is creeping up. MIMS recommends that after 100 mg/5 days:

> If ovulatory menses do not occur, this dose may be repeated for 2 additional cycles, but *failure to induce ovulation after 3 consecutive cycles* at this dosage *should constitute an adequate therapeutic trial.* If, however, ovulation does occur at this dosage but is not followed by pregnancy, subsequent courses for a total maximum of *6 cycles* of Clomid treatment may be administered (1987: 373; our emphasis).

With respect to repeating the therapy, they write in 1984 that long term cyclic therapy is not recommended: 'Clomid cannot be recommended as monthly maintenance therapy for patients whose ovulation defects recur when treatment is discontinued because the safety of long term cyclic therapy has not yet been conclusively demonstrated' (p. 326). Yet by 1987, this warning has been dropped from the description.

In Klein's (1988a) Australian IVF study of 40 women who had used IVF, 12 women were on 50 mg Clomid daily – the dosage recommended by the manufacturer – 15 women took 100 mg per

day, and 4 women were given 150 mg daily. The administrations were usually for 5 days at a time, yet two women remember 6 days on 100 mg and one woman was on 50 mg per day for *one year.* Another woman commented:

> I started with one tablet a day but when the ultrasound check up revealed that my eggs did not grow properly, I was told to increase the dosage to *four* tablets a day. The attempt had to be abandoned: my ovaries swelled considerably and despite injections to release ripe follicles no mature eggs were recovered (our emphasis).

This finding – that dosage was increased if no follicle growth occurred – coincides with a Canadian researcher's view. Jane Roberts, an epidemiologist said that she believed dosage levels for Clomid in IVF treatment were arbitrarily set and that the dosage was increased until the desired number of eggs were obtained (in Pappert, 1988).

The medical research literature confirms that a great deal of 'flexibility' is exerted by researchers in their experimental trials on women. For example, Yee and Vargyas say in their review (1986: 142); the most widely used regimen in normally ovulating women undergoing an IVF treatment cycle is 100 or 150 mg/daily from cycle day 5 to cycle day 9.' They list studies by Quigley *et al.* (1988), Marrs *et al.* (1983), an Australian study by Lopata (1983), and their own work where 150 mg/day have been used on one group of women, in an attempt to compare the success rate with those receiving 100 mg/day. Messinis *et al.* (1986) report that they also had 14 women whom they had put on 150 mg daily for 5 days.

It seems that IVF practitioners themselves do not always adhere to the guidelines recommended in the MIMS for dosage level of clomiphene. This is also demonstrated in conventional infertility treatments. Pfeffer and Woollet quote the case of a woman who said (1983: 82): 'I was on Clomid for about 9 months . . . they increased the dose twice.' Two others took Clomid for six and nine months, respectively with varying dosages.

One particularly blatant case is reported by Titia Esser in Holland (Rowland, personal communication, 1987; in Klein, in press). After administration of one tablet a day for a five day period she was put on two tablets a day. After she had taken this dosage for six months, her gynaecologist put her on three tablets a day. This induced ovulation, but also terrible side effects. She reports that after three months on this treatment her regimen was changed again:

> I had to take one tablet on the first day of treatment, two tablets the second day, up to five tablets a day.

During preparation of this paper, a woman wrote to us indicating that she had been on Clomid for 8 *years.*

It is more difficult to establish how many and which kind of hormones are given to the women. As one Australian woman comments (Klein, 1988a):

> I don't know the name of the hormone injections. We were not told. The number of injections and the day(s) of the cycle on which they were administered varied from patient to patient.

Yet some women said they received HCG injections for 10 days per cycle and one woman reported 68 hormone injections in five IVF treatments. Out of 40 women, 35 were given hormone injections before egg collection: 28 at one per day, 7 two per day.

Maggie Humm, a woman who describes her treatment for amenorrhoea in Britain *did know:* she had appropriated the houseman's notes. Clomid did not work for her. She writes (Humm, in press):

> The increased dosages gave me only migraine and dizzy nauseous reaction to bright lights and walls but *not* a stable cycle.

Clomid was followed by intramuscular HCG injections (Pregnyl) for five days a month but it was not successful. She moved on to HMG (Pergonal) injections in connection with Pregnyl when the egg was considered ripe. The intramuscular Pergonal injections were most painful and complicated by the daily urine collection to assess its dosage. This regimen ended in her being rushed to the hospital. Hyperstimulation of her ovaries had occurred. In her own words:

> The day after an increased dosage my waist size increasing one inch every hour, breathing asthmatically and my legs swelling

> perceptively, I was admitted to the Casualty Ward. In the 'For Hospital Use Only' booklet I stole earlier from the hospital it said, severe hyperstimulation – pleural effusion, intramuscular thrombosis, multiple pregnancy.

5.2 'Side effects'- and the doctors' responses

When one Geelong woman told her doctor that she felt: 'depressed, spaced out, lethargic and over-emotional' the gynaecologist said this was an unusual response (Rowland, personal communication, 1987). And Titia Esser (in press) remembers that her doctor thought it would be fairly easy for her to conceive with a small dose of Clomid. She says: 'In his opinion Clomid was an absolutely safe medicine. He had been prescribing it for several years without complaints or problems worth mentioning. The only drawback he could think of was the possibility of a multiple pregnancy.' Yet Titia Esser's 'side effects' began with a 'constant vague pain in my belly which I tried not to feel.' She goes on to say:

> After having used three tablets a month I couldn't deny the side effects any more. I had dizzy spells, a constant pain in the left side of my belly and a funny feeling inside my head . . . I couldn't see sharply any more. I saw lights and colours and I felt kind of strange/funny inside my head. I remember one time at school when I began to panic because I couldn't see clearly. It made me feel unbalanced and insecure. While working with pupils I suddenly couldn't remember the simplest things. Was that a side effect of the drug as well? I almost couldn't believe it. I also suffered from a pain in my belly which dragged on and on. Emotionally I wasn't stable any more (Rowland, personal communication, 1987; Klein, in press).

In Australia, a Geelong woman who had been given Clomid for six months was suffering from chronic diarrhoea, nausea, headaches and depression and had to have an ovarian cyst removed (Rowland, personal communication, 1987) – a worrying incident that we have heard of again and again during our research.

Developing cysts which necessitated stopping IVF were reported by 9 women out of the 40. As one woman who was on 100 mg of Clomid for five days for one year including 10 days per cycle of HMG injections for twelve months said: 'I had to have yet another laparotomy when I was superovulated and developed very large ovarian cysts from clomiphene' (Klein, 1988a).

Another woman, notably with a low Clomid dose (one tablet daily for three days) said: 'My body did not respond to hormone therapy in a positive way. I developed a cyst which caused more problems.' And a third woman in the Australian study who had been given 50 mg of Clomid for five days said:

> My third attempt: 16 eggs good size, when pick up happened found cyst, lost eggs except one. No success. I was told my cyst had killed off my eggs, but when I was unclear they told me they had drained my cyst and I could come in on my next cycle. After going home and having much pain I went back to my own doctor and was told I would have to go into hospital and have the large cyst removed. I also could lose one or both of my ovaries. I was very upset with this because it meant 10 days in hospital, 6 weeks off work and my fourth long operation.

Other women developed enlargement of the ovaries, ovarian abscess and septicaemia and some reported bleeding constantly. Dizziness, nausea and feeling 'very ill' are 'side effects' women on these drugs report with almost no exceptions. Visual problems often occur too. A woman whose initial dose was doubled, reports (in Davidson and Rakusen, 1982: 108):

> By this time I had discovered that my eyes were being affected. I had gone to the optician worried about my eyesight and was asked if I was on any drugs. He told me that the drug [clomiphene] *could have six possible side effects on the eye alone* (our emphasis).

For some women these adverse affects do not stop when they abandon IVF. As one woman comments (in Klein, 1988a): 'I have had two operations, the first was a hysterectomy, the second a removal of a cyst on the remaining ovaries.' Another woman states that she has been ill since she left the IVF programme:

> I felt depressed for weeks following the failure of my second attempt. Emotional, unable to

> cope. Very lethargic, tired. Headaches. Bloated stomach, irritated. Continued to superovulate for at least two or three months afterwards. Pre-menstrual tension effects tripled. The worst was the continual DIZZINESS–began on the second day of the injections and only gradually improved. Even now, three months later, I still feel dizzy if I overdo things. For the first two months it was terrible. Three months after my first attempt I bled for three weeks and was very ill as I developed a severe bronchitis at the same time. Now I have a rash – three months after my second attempt. The bleeding episode in June last year was very unusual for me – my GP said it was probably connected to the IVF treatment.

These are serious demonstrations of ill-health after administration of clomiphene. And the women were not *informed* prior to these procedures about potential health hazards. In a study by Burton (1985), one woman on the IVF programme gives us an idea of why this might be:

> The professor tells us that according to the labels and his books they don't have side effects. Once someone comes out and is brave enough to say you get side effects, other women say so too. I think that's what he's worried about, that side effects are catching.

5.5 *Were the women informed?*

For many women thinking back on their infertility history, the administration of Clomid and in many cases Pergonal is mentioned almost as a side issue in the long trail of treatment. Christine Crowe (in press) reports the case of an Australian woman who in between monthly dilations of the cervix, three laparoscopies, an operation to remove adhesions from her ovary, surgery to remove fibroids on the outside of the uterus and surgery to correct a retroverted uterus, swallowed Clomid and received Pergonal without ever being informed about potential adverse effects (in Klein, in press). Another Australian woman with a similar history remembers (in Klein, 1988a):

> I wasn't told anything about possible side effects of the Clomid tablets (and later Pergonal injections). When I felt sick, bloated and dizzy all the time I thought it might be because of my anxiety to do the 'right' thing: to have sex at the 'right' time, to think positive, to relax. I was very moody during that time and it was a great strain on our marriage. I didn't feel I could talk to my GP about it ... I felt like it was all my fault: my body would not only not produce eggs it also made me sick ... I felt dreadful.

Given the explicit 'adverse reactions' described in the MIMS that can occur after Clomid administraion, the failure of doctors to inform their clients must be viewed with extreme concern.[11] So too should books on infertility such as *The Experience of Infertility* (Pfeffer and Woollett, 1983) where there is *no* mention of side effects in the two page description of Clomid (pp. 82–83).

Women on IVF programmes are not informed either. In the Australian IVF study, out of 40 women only 9 said there was a discussion of potential side effects from the hormones during IVF. When side effects *were* mentioned, however, information only included the following: 'Hormone levels will be affected' (1) 'Not a great deal of side effects' (1), 'Multiple births possible' (2), 'Lots of eggs will be produced' (1), 'Dizziness/nausea' (2), 'Weight increase' (1). One woman was just told 'not to worry.' Only one doctor mentioned, but dismissed, the potential long term side effects. The woman was told: 'It is a new science . . . we are not aware of potential long term side effects.' Ten women commented that they *were worried* about possible effects from the drug. Some of them looked for further information, feeling that they were 'guinea pigs.' Yet Titia Esser from Holland speaks for many women when she says (in Klein, in press):

> I hadn't heard of Clomid before in my life. One of my girlfriends, a nurse, warned me. She explained that hormone-drugs could be dangerous. At that time I didn't know what to do with her words. I desperately wanted to believe the gynaecologist. *He was the authority and I thought he would know best,* (our emphasis)

Her words reflect the difficult position women are in when they and/or their partners turn to reproductive medicine for help. They trust that the experts will know best, act responsibly, have the women's best interests at heart. Our findings imply

that contrary to this, women are used as living test-sites for fertility drugs.

6. WOMEN AS TEST-SITES

Our own research as well as the review of the scientific literature confirm that reproductive medicine uses women as 'living laboratories' (Rowland, 1984: 364). This is not a new discovery in terms of the relationship between medicine and women. We know that experimentation with drugs like Thalidomide and DES have led to various court actions against pharmaceutical companies. The issue of informed consent with respect to women on medical programmes seems rather ludicrous (Rowland, 1986). It is horrifying that practitioners such as Dr. David Healy (1987) can write dismissing the scientific evidence on this drug, while continuing to administer it to women whom he assures about its innocence. We agree with him on only one point: *'It is concerning and unacceptable that these scientific errors continue to appear in print.'*

It is also clear from the summary by Yee and Vargyas (1986) that many of the hospital programmes run experimental trials with women seeking IVF. The outline of research done with the administration of these drugs indicates that women are deliberately separated into various control and experimental groups. For example, in Australia, studies reported by Lopata *et al.* (1983) show that these doctors changed their regimen of drug combinations for various groups of women in order to see which were the most 'productive' in producing a decent egg 'harvest.' The deliberate use of women on IVF programmes as experimental laboratories is summed up by a recent French medical text (Hedon *et al.,* 1986):

> IVF is a remarkable instrument for testing new ovulation procedures thanks to: the parameters it allows to be controlled; *the number of women who can be treated.* Lastly it enables controlled series to be carried out which compare the new therapeutics with "routine" stimulation protocols. *It no longer appears possible to consider the marketing of new drugs for stimulating the gonado-pituitary axis unless they have been tested within the framework of IVF (OUT* emphasis).

The question here is, are the women informed about the possible side effects and dangers of these drugs? Are they informed that sometimes they are given twice or three times the normal dosage recommended by the MIMS? We doubt it. In a revealing comment Yee and Vargyas write (1986: 141):

> One of the challenges facing IVF centers today is the need to identify those protocols leading to multiple follicle development and in turn produce multiple embryos *without detrimental influence on the establishment of clinical pregnancies* (our emphasis).

Outrageously, the safety of those protocols for *women,* or the children born at the end of the pregnancy, are not even mentioned. It confirms that the women are seen as experimental raw material.

These issues become even more pertinent as profit making enters the picture. Pharmaceutical companies are established in order to make profit, not to assist infertile women. Discussing the role of these companies and their relationship to women, Anne Rochon Ford points out that the manufacturing of synthetic estrogen alone has meant that $80 million worth of estrogen is dispensed annually in estrogen replacement therapy in the United States (1986: 36).

Serono Laboratories Inc., which is the sole supplier of Perganol in America, had sales in 1986 of $35 million, up from $7.2 million in 1982 (Blakeslee, 1987). This kind of profit can motivate doctors and pharmaceutical companies to take the 'wait and see' approach which is being advocated in the medical literature. Unfortunately, those who may be the victims of this 'experimental methodology' of trial and error, may be the women who are taking the drug and their children.

Ironically, and perhaps in the most gross sense of experimentation, the daughters of women exposed to DES who are suffering from infertility due to physical abnormalities, who have repeated ectopic pregnancies, or who are unable to carry a child to term, are being encouraged to join IVF programmes. In one study, these women were superovulated using hormonal cocktails (Muasher, Garcia and Jones, 1984).

Science's modus operandi – to continue experiments until mistakes have been statistically proven – is unacceptable to us when the lives and

health of women and their prospective children are at stake. In fact we posit that it is ethically irresponsible. From our analysis of the scientific literature and our own research discussed in this paper, it is our contention that clomiphene citrate – alone or in a 'cocktail' with other synthetic or natural hormones – are a dangerous health hazard for women. *They should not be administered to women and should be withdrawn from use.*

The problem of infertility must be assessed differently. Conventional fertility treatments and IVF programmes perceive infertile people as 'machines' with 'defects' that need to be corrected. Such an approach does not work, and, as we have shown, uses living human beings as experimental material, thereby harming many of them. IVF – in all its forms – must also be abandoned. It is a failed and dangerous technology. And it provides a vulnerable population of women on which to continue experimentation.[12] In the words of Canadian researcher Anne Rochon Ford (1986: 39):

> In our lifetime, we have seen birth deformities from thalidomide, vaginal cancer from DES and infertility from the Dalkon Shield IUD. How many more discoveries like these will it take before the parties involved – the pharmaceutical industry, doctors, and patients – realise that they are a part of a continuum.

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ENDNOTES

1. Letter to the Editor of the *Herald,* Melbourne October 15, 1987 in response to Robyn Rowland's article 'Women the silent victims of IVF research,' *The Herald,* October 2, 1987. Furthermore, in an article by Sonja Voumard in *The Age* (June 20, 1988) in response to our conference paper presented at ANZAAS, Professor Pepperell, again from Prince Henry's Hospital in Melbourne, said that 'he was confident the drug [clomiphene] was being used safely and appropriately'.

2. While scientists continue to misrepresent their technology as effective by using the term 'success' rates, we prefer to indicate the more accurate failure rates of these procedures. Transposing official figures, 'failure rates' are 91.5 percent for Britain for 1985 (VLA Report, 1987: 15); 93.2 percent for France for 1986 (Laborie, 1987: 50); 92.6 percent for Australia for 1986/7 (Bartels, 1987: 474). Recent unofficial figures indicate that the 'real' success rates might even be only between 2 and 4 percent (Marcus Steiff, France and Christine Hölzle, West Germany, both personal communication to Klein, April 1988). For a general overview of how 'success rates' are manipulated by IVF clinics, see Corea and Ince (1987).

3. Subfertile men with healthy functioning fertile partners are a rapidly expanding category of IVF clients. Laborie (1988) reports 16 percent of IVF clients in France for 1986/87 fall into this group. An Australian doctor recently said at a public forum that as many as 30 percent of his clinic's IVF 'patients' are there because of male infertility (Ferber, personal communication to Klein, April 1988).

4. We are aware of ongoing research (e.g., in Australia, North America, and Britain) to try and mature immature eggs *in vitro,* and it is another area we watch with great concern. It would place even more control in the hands of doctors and scientists who could 'help themselves' to slices from women's ovaries in connection with hysterectomies and other operations. An endless supply of eggs to experiment with would indeed be the 'egg heaven' British IVF pioneer Robert Edwards dreamt of when he was experimenting with IVF technology 10 years ago (Corea, 1984). His desire may soon come true (the perfect test-tube calf has already been produced in Ireland; Vines, 1987). In Australia, work with follicle growth factors (GFs) has led Dr. Max Brinsmead to discuss maturing eggs *in vitro* as possible, not only from slices of ovaries taken from women, but also from female fetuses at the 14th week (Miller, 1988). The implications of the maturation of immature eggs *in vitro* is discussed elsewhere (Klein, 1987; 1988b; Bartels, 1988). But even if this new procedure were perfected, women would still be used as 'living laboratories' (Rowland, 1984) into which the man-made embryo will be inserted, unless of course, the artificial womb is perfected too. Then reproductive technology could claim total independence from women's procreative powers.

5. This information is from *Our Bodies, Ourselves* (1985): 209–10.

6. *IVF and GIFT pregnancies in Australia and New Zealand, 1986.* National Perinatal Statistics Unit, Sydney, Australia, November 1987.

7. As in footnote 6.

8. Together with the increasing tendency to detect 'anomalies' early in pregnancy through embryo biopsy (see Bartels, 1988), it must be feared that in the future disabled people will have an even harder time finding a place in society where they can develop their potential to the fullest, since it might be argued that they could have been 'avoided.'

9. Calling women in conventional or IVF treatment 'a population of fertilisation failure' demonstrates clearly the lack of respect with which infertile women are confronted once they entrust themselves to reproductive medicine. Furthermore, in many cases this term is a misnomer: many of the women are fertile and on programmes for their male partners' infertility problem. And those women whose

problems are due to iatrogenic infertility (e.g., infections due to IUDs) could rightly be outraged at being called 'fertilisation failures.' This statement is indicative, as we discuss in the text, of 'blaming' women rather than searching for the real cause of the problem in the medical procedures employed and the drugs associated with them.

10. Personal Communication Professor Eylard Hall to Rowland, August 4th, 1986.

11. Whether in conventional infertility treatment or on IVF programmes, invariably the women are called 'patients.' This contributes to the idea that a person with a fertility problem is sick. We hold that infertility is not an illness and is not life threatening. We therefore prefer the term 'client.'

12. This experimentation continues with newer drug regimes. New drugs such as agonists of LH-RH — (e.g., Buserelin; see Laborie, 1988) put women into chemical menopause so that they then can be started 'afresh' with ovulation stimulants (FSH and HMG). We know already that one of the 'side effects' of Buserelin is heavily hyperstimulated ovaries. Furthermore, though little research has been conducted, it is already extensively used in France on large numbers of women in IVF programmes (Laborie, 1988 and personal communication, 1989). It is to be feared that Buserelin will soon be used in Australia too, as announced in June 1988 by the chairman of the Epworth IVF unit, Dr. Mac Talbot. Sonja Voumard writes in *The Age* (June 20, 1988): ' . . . Dr. Mac Talbot said it was hoped the new treatments, buserelin and metrodin would yield better pregnancy rates.'

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