AN INTERVIEW WITH DR. HUGH GORWILL: POTENTIAL RISKS TO WOMEN EXPOSED TO CLOMIPHENE CITRATE

ANNETTE BURFOOT
Department of Sociology, Queen's University, Kingston, Ontario, Canada K7L 3N6

Synopsis – An interview with Dr. Hugh Gorwill, a practicing gynaecologist and obstetrician, and researcher in the area of reproduction, reveals the nature of research on the hyperovulatory drug, clomiphene citrate. A potential link between the drug and DES is explored but dropped after initial findings prove no substantial relationship. The problem of risk assessment of hyperovulatory drugs is revealed as fundamental to scientific rationality in medical research, leaving the well-being of women and their children at risk.

Dr. Hugh Gorwill is a medical practitioner and researcher, who from 1982 to 1988, investigated potential risks to women exposed to the hyperovulatory drug, clomiphene citrate (Gorwill et al., 1982, 1988). The studies used mice as a developmental model for women and the findings indicated that pathological effects, especially in the walls of the vagina, arose from exposure to clomiphene citrate. The study proposed that the chemical structure of clomiphene citrate is similar to diethylstilbestrol (DES), the drug used on pregnant women since 1941 in the United States and that has since proved to cause reproductive tract abnormalities and cancers in their daughters.

Clomiphene citrate, also known by its pharmaceutical name, Clomid, is routinely used in in vitro fertilization and gamete in-tra-Fallopian transfer as a hyperovulatory drug. It is also used as a fertility drug to hyperovulate women who do not necessarily undergo in vitro fertilization and gamete in-tra-Fallopian transfer to stimulate ovulation.

The following interview was conducted in Kingston, Canada on 19 June 1991. The purpose of the interview was to discuss Dr. Gorwill's research and to see why his funding into the pathology of clomiphene citrate use ended. In the course of the discussion. Dr. Gorwill reveals the reasons for his studies and makes some points regarding the use of thalidomide at the time clomiphene citrate entered the Canadian drug market. Gorwill's explanation for the decline in funding of risk research of hyperovulatory drugs is related to a general problem of underfunding in reproduction. However, given that dangerous effects of hyperovulation continue to be reported (usually in a spotty manner and in regard to immediate effects only; Grenman et al., 1990; Chaudhuri et al., 1990; Tani et al., 1990) and that trends in the field of reproductive medicine increase women's exposure to hyperovulatory drugs and hormones (de Wit et al., 1991), there remains a poverty in research of risk assessment especially over the long term. Typically, as a researcher in medicine and the science of reproduction, Gorwill does not pursue the wider issues involved in new reproductive technologies, which include linking the effects of hormone and drug cocktails, repeated surgical procedures used on women in the pursuit of pregnancy. Also, the balance between research on immediate detrimental outcomes versus long-term effects continues to be weighted in favour of the former.

IRAGE: What can you tell me about clomiphene citrate?

GORWILL: Clomiphene citrate came on the market in 1961 as a method for inducing ovulation in the anovulatory, which was obviously a long time before (new) reproductive technologies. It was used (as a hyperovulatory drug) in various regimes ever since. Its use in in vitro fertilization to produce multiple ovulation or timed ovulation obviously paralleled the growth of in vitro fertilization programmes.

IRAGE: When it came on the market, had there been any testing for the potential long-term effects of its use?

GORWILL: Am I aware of what was necessary to market it in 1961? . . . Specifically, I don't know what was in the application, but yes, there were things that (the manufacturers) were required to present for licensure. Bearing in mind that 1961 was (also) the year that Kevidon was on the Canadian market. . . . Kevidon is the trade name for tha-lidomide. It never got on the American market either because the American Food and Drug Administration was wise or because it was so bureaucratic and slow that they never got around to it. The implication that I am making is that whatever the requirements were for licensure of clomiphene in 1961 in the United States, they were different than they would be now.

IRAGE: What did you see as problematic with clomiphene?

GORWILL: This series of papers (Gorwill et al., 1982, 1988) arose because of my concern that the two components of clomiphene citrate look like DES when they are put down on paper. If they look like DES and they are estrogenic, they might act like DES. By this time (1977), the DES story was well developed – it started in 1970. In the next year (1971), the first paper appeared in which strange vaginal carcinomas were defined in numbers in teenage girls. The question that I asked was simply, "How does clomiphene act in available experimental models? Does clomiphene act the same way (as DES)?" You know and I know that if you give DES to a human mother bearing a female child at the right time it will increase the incidence of vaginal adenosis in female children born thereafter and it will increase the incidence of vaginal carcinoma.

IRAGE: What study are you referring to?

GORWILL: A bunch. There are all kinds of studies.

IRAGE: The only one I can find is Japanese (Anderson, 1988).

GORWILL: With respect to DES? . . . DES is associated with adenosis and subsequent vaginal carcinoma. . . . Vaginal carcinoma is very uncommon so you are not going to use human experimental subjects to see how often anything happens in a similar group. So I simply asked the question here, "Suppose you gave DES to newborn mice?" You know that DES is a carcinogen in mice. Then, in parallel lines of animals give clomiphene citrate to newborn mice to see how they evolve in comparison to the DES group. That is the essence of this study.

Now, you were raising questions of Japanese data with respect to?

IRAGE: I am aware of one study in Japan that showed a similar link between DES and female child cancers and clomid use on women on a long-term basis and a higher incidence of rare vaginal and cervical cancers in their daughters.

GORWILL: Obviously, if that's credible, these reports link. I was referring to mice. If you set out to identify that DES causes vaginal

carcinoma, since it is not common, you'd have to feed DES to a whale of a lot of women . . . in fact, in the United States that happened. It didn't happen in Canada.

IRAGE: However, with clomid, surely you have a large body of women now who have been exposed to it during in vitro fertilization and gamete intra-Fallopian tube transfer?

GORWILL: Yes, or treated pre-in-vitro fertilization. The in vitro fertilization ones are exposed to higher doses.

IRAGE: Is there anything interesting in the use of clomid in combination with gonadotrophins?

GORWILL: Well, there are all kinds of questions that are unanswerable. What was a further interest of mine was that clomiphene citrate given to the mother to induce ovulation is a drug that has a long half-life. You could see the possibility that the drug may still be present in the mother during male and female reproductive tract development.

IRAGE: Can you give me a sense of what this large amount is in terms of relative amounts in natural hormonal cycles?

GORWILL: There is no clomiphene in a natural cycle.

IRAGE: I know, I am trying to get a sense of what the impact of these hormones is. For example, compare the impact of clomiphene with the use of hormonal contraceptives. I know it is all apples and oranges, but it is similar in the sense that you are exposing the same system, namely the female reproductive tract, to various hormones at roughly the same level of hormonal activity (the level of reproductive organs).

GORWILL: You have to bear in mind that *natural* hormones in mothers during pregnancy have natural metabolic mechanisms. The placenta metabolizes hormones, to protect the foetus from things inside the mother. Drugs that are not natural may not be metabolized in the same way, so there may be no protective mechanism.

IRAGE: You attempted to look into this in mice. The purposal was to inject baby mice with DES and clomiphene?

GORWILL: I did that study. It was funded by the National Cancer Institute of Canada. The second one was funded by the Medical Research Council of Canada.

IRAGE: Which one did not get funded?

GORWILL: A subsequent proposal in the same vein as the others still working with mice. I think it is important that I don't see any sinister conclusion in that fact. That's the way research funding goes. It is peer reviewed.

IRAGE: Do you think that there may be a renewed interest in this subject given that there is now a Canadian Royal Commission on New Reproductive Technologies that is highlighting gaps in our knowledge of new reproductive technologies and their potential risks?

GORWILL: Two things. If the study you identify in Japan is true; it bears scrutiny, yes there's going to be an interest. I am surprised I haven't heard of it – I'm saying it probably isn't true. The second issue, which is more important, is that very little money goes to reproductive physiology. In fact, we know more about what makes females work than what makes males work. That's only because females create population problems.

IRAGE: Females create population problems? How do they do that?

GORWILL: The common pathway to turn off having people is females.

IRAGE: But we don't create the problem.

GORWILL: Well, just accept from where that came. The other important reason for knowing about reproductive biology particular to the female is the cattle industry. Cows are important; bulls can be replaced. These days bulls are so unimportant that you can collect the ejaculates and divide them and freeze them and use them forever so you don't even need a bull. Put in its crudest terms, the reason why we have the knowledge we do is because of the need for this reproductive physiology. It has nothing much to do with fertility. The question is whether or not the Royal Commission will create a different research environment. I doubt it.

IRAGE: I am amazed that this has garnered public attention for such a long time. We have been talking about test-tube babies for over 10 years now.

GORWILL: It is public attention but it is the kind of stuff that fills the nooks and crannies of newspapers. Just because the public is interested doesn't mean they want to put money into reproductive biology.

IRAGE: I think it does help to have it in the public light.

GORWILL: The half-life of research is a very long time. The question is, are we developing the people to do reproductive research in the future? What funding does reproductive medicine have now? In this country it is a tad depressing. The Medical Research Council of Canada gives less than 5 % of its funding to reproduction.

IRAGE: You have dropped this research?

GORWILL: I am not now involved with that work. These are the two major publications that came out of that work (Gorwill et al. 1982, 1988). In the first study, we identified striking similarities of the effects of DES and clomiphene citrate in the murine (mouse) vagina. In the long term, we watched mice for more than a year and saw that the effects of clomiphene and DES were quite different. The end result did not bear out the concern I initially had. But what you are saying about the Japanese study is different?

IRAGE: It could also be that DES and clomiphene citrate will not have the same effect over the long term, but both may have toxic effects.

GORWILL: Whatever you mean by toxic effects.

IRAGE: Carcinomas found elsewhere in the reproductive tract, for example.

GORWILL: Sure, I was only looking at one system. There is everything else.

IRAGE: I know that there is discussion of a relationship between clomiphene combined with gonadotrophins and ovarian tumors.

GORWILL: Yes, I have seen some of that. The question is whether this is an association or cause and effect. Also bear in mind major congenital abnormalities occur in humans at a rate of 2 to 3 % without any use of drugs.

IRAGE: There are also environmental factors, such as proximity to nuclear power plants. Also, I think it would be interesting and relevant to do longitudinal studies of women exposed to in vitro fertilization and gamete intra-Fallopian tube transfer programmes to see if there are any correlations between the drug regimes they went through and particular types of outcomes.

GORWILL: And it would be very expensive.

IRAGE: There is the information available - drug regimes and women's identity are routinely recorded in IVF clinics.

GORWILL: The database is there, but it takes money to contact the woman after long periods of time and to do the study.

IRAGE: I see. Thank you for your time.

REFERENCES

Anderson, lan. (1988, January 14). Birth problems linked with fertility drugs. *New Scientist*, p. 32.

Chaudhuri, C., Mukherje, M., & Chakrabo, B. N. (1990). Biochemical studies following ovulation induction with Clomid and human menopausal gonadotrophins in infertile Indian women. *International Journal of Fertility*, 35(1), 58–64.

de Wit, Cynthia, & Ewing, Christine. (1991). News on developments. *Issues in Reproductive and Genetic Engineering*, 4, 179-200.

Gorwill, R. H., Steele. H. D., & Inder S. R. (1982). Heterotopic columnar epithelium and adenosis in the vagina of the mouse after neonatal treatment with clomiphene citrate. *American Journal of Obstetrics and Gynaecology*, 144, 529–532.

Gorwill, R. H., & Steele, H. D. (1988). The long-term effect of clomiphene citrate on vaginal epithelial differentiation in the mouse. *Reproductive Toxicology*, 1, 263–266.

Grenman, S. E.. Salmi, T., & Meurman, L. (1990). Postmolar trophoblastic disease following coexisting molar pregnancy and living fetus subsequent to clomiphene citrate therapy. *International Journal of Gynaecology and Obstetrics*, 32, 381–385.

Tani, H., Oda, K., Schichir, K., Arakawa, O., & Sato. Y. (1990). Combined intrauterine and tubal pregnancy after in vitro fertilization and embryo transfer. *International Journal of Gynaecology and Obstetrics*, 33, 359–363.