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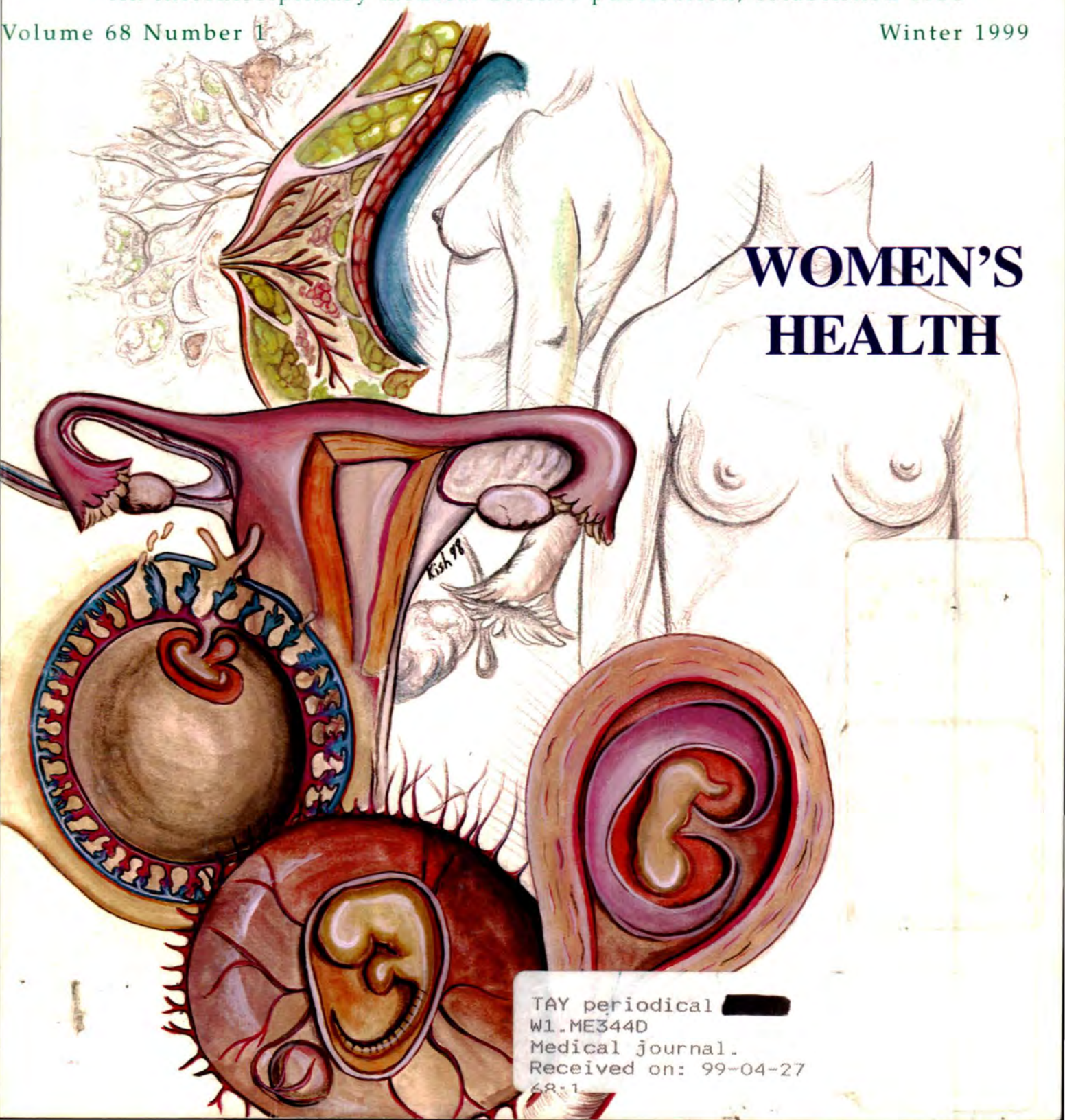

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2. Toft AD. Thyroxine Therapy. NEJM 1994;331(3):174-180.

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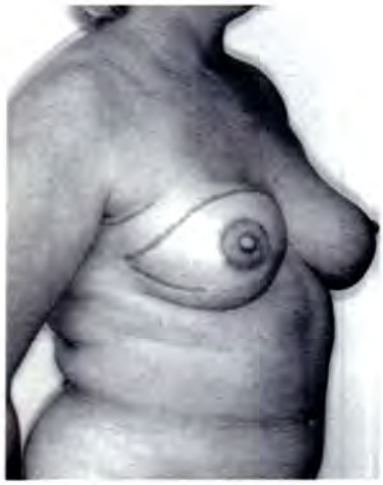

Restauration of Self Through Reconstruction of Form

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EDITORIAL

THE CHANGING REALM OF WOMEN IN MEDICINE

By Aaron M. Glickman & Carla Garcia

One of the reasons that this particular volume was assembled was the need to recognize the changes that North American women have gone through in all aspects of contemporary life. This is clear here at the UWO Faculty of Medicine simply by the quantity and breadth of the material submitted for the topic of Women's Health for the UWO Medical Journal. Although many of these changes have brought women greater benefits, it has also brought greater risks particularly with regards to their health.

The topic of 'women's health' has meant a wide variety of things to a wide variety of people over the centuries. Until relatively recently, women's health meant obstetrics and gynecology, putting women in the unenviable position of being viewed medically only in the context of their reproductive role.[1] As a result, solutions to women's health needs had been limited to improving maternal and child health, while ignoring the wide spectrum of other health concerns that enter a woman's life. However, it soon became apparent that 'women's health' not only encompassed much more than reproduction, but also influenced a larger spectrum of the population than the previously targeted reproductive female. Indeed, the pendulum has swung recently so far to the other side that some women's groups are complaining that 'women's health' has become an umbrella term for everything from pediatric health to geriatric health to global health trends.[2] This incredibly broad spectrum of influence can be at least partially explained by the extremely important roles women continue to play in nearly all societies as primary caregivers in the home. The care of society's dependants—children, the elderly, the infirm—continues to fall upon the shoulders of women,[3] and health organizations such as the WHO, have come to realize that women—and their health—thus have a very direct effect on these segments of the population's health care1.

However, this significant role as caregivers comes in addition to increasing work hours outside the home, and, in North America, increasing age of this population of caregivers.[4] Thus, it is not surprising that women are experiencing an increase in chronic diseases, eating disorders, depression, stress-related illnesses, physical and substance abuse, etc.[1,4,5] This situation is compounded by the fact that neither the medical profession nor society nor women themselves appear well informed on certain aspects of their health. For example, both lung cancer and smoking continue to rise alarmingly in women, despite efforts at education and prevention,[6] and only recently has the medical community come to accept that female pulmonary physiology may indeed vary significantly from the 'standardized male' values that all patients are traditionally measured against.[7] In fact, that same medical tendency to treat women based on data collected from males has developed into a significant obstacle on many fronts, and recent studies have found a wide variety of gender specific differences that are currently not being accounted for properly in the treatment of women.[8]

Perhaps the most worrisome combination of ignorance on the part of women, their healthcare workers, and society at large is observed in the management and outcome of ischemic heart disease in women vs. men. The misinformation exists at every level. Clinical trials evaluating drug therapy for IHD do not adequately represent women (even those that claim to have gender-related policies).[9] Physicians tend to diagnose women with IHD later than men, and tend to refer them for bypass surgery at a much more advanced disease state than their male patients,[10,11] which may help to explain the fact that women's outcomes and prognosis are significantly poorer than men's for this disease. Women are similarly misinformed about their relative risk for heart disease,[12] and in fact, many were under the impression that their gender reduced the risk of cardiac disease to the point of inconsequence, and took few if any preventative measures.[13] Fortunately, previous misapprehensions are being corrected, and there have been great strides in the education of both women and their health care providers in both the treatment and prevention of IHD. Two papers in this issue deal with post-menopausal hormone replacement therapy, and its emerging role as a cardioprotective agent in high risk women.[14,15]

This naturally leads to the inevitable question—how well are we as students being educated in women's health? As several of the papers in this issue reveal, there are certainly significant gaps in our current curriculum. For example, Briar Sexton's paper[16] discovered a startling lack of formal training for one of the most important clinical skills in women's health—the breast exam. Baugniet *et al.* found that their workshops on menstruation filled a significant knowledge gap in both young girls and medical students.[17] Tess Pitre comments in her article on the consequences of lack of physician knowledge with respect to breastfeeding and neonatal nutrition.[18] Jim Grochowski's paper emphasizes the important role that emergency room physicians play in the management of spousal abuse (which remains one of the greatest threats to women's health), and yet there was

little formal training on this subject in the old curriculum—a situation which has fortunately been corrected in the new system at Western.[19]

However, despite these still-lingering problems, great strides have been made in other areas of women's health. Three articles in this issue deal with the progress that has been made in the prevention, diagnosis, and treatment of breast cancer.[20,21,22] In particular, Mason. Ross' article on breast reconstruction is an excellent example of medicine assisting women in their physical and psychological recovery following mastectomy.[22] Rupinder Singh Sahsi has found a wealth of useful, accurate information for women and health care professionals alike on the internet.[23] The increasing presence of women in medicine have also lead to significant changes in both how the profession views itself and its female patients—an issue which is addressed in Rodin & Saibil's paper in this issue.[24] And, the profile of Dr. Nisker reveals a physician educator who has made a great effort to educate medical students and faculty at UWO about one of the most tenuous realms of women's health—the ethical issues surrounding current advances in fertility treatments.[25]

Thus, the scope of this issue remains necessarily broad, in an effort to reflect some of the span of topics that fall into the domain of women's health. While a complete, thorough review of this area of medicine would be near-impossible, it is our hope to present a collection of articles reflecting some of its recent triumphs and more pressing concerns.

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PROFILES

EDITOR: HELEN LEWANDOWSKI

INTERVIEW WITH DR. JEFF NISKER

Professor of Obstetrics and Gynecology and Coordinator of Bioethics at the University of Western Ontario Faculty of Medicine

By Helen Lewandowski, MEDS 2001

INTRODUCTION

Dr. Jeffrey Nisker is a Professor of Obstetrics and Gynaecology at the University of Western Ontario who was recently chosen by the CBC's Peter Gzowski as one of the 13 "Best Minds of our Time". Perhaps this is because Dr. Nisker wears many hats in addition to his hat as a clinician. He has won international awards for his research into how cancer can be caused or prevented by hormones, and has done work for Health Canada Commissions in the area of reproductive technologies. He is also the initiator of a novel approach to address ethical issues through plays, stories and poems. He believes that in an age of shrinking health care resources, clinicians and health care students must find ways to retain their empathy for their patients and deliver optimal compassionate care. According to Dr. Nisker, "theater and poetry and song...can put us in the skin of a patient and approximate empathy for that patient". When interspersed throughout medical education, Dr. Nisker believes that this approach can help medical students retain the intelligence, compassion and courage, which they possess upon entry to medical school.

Dr. Nisker received his undergraduate and medical education at the University of Toronto, and his training in Obstetrics and Gynaecology at the University of Western Ontario. He was awarded a Medical Research Council fellowship in hormones and cancer and did post-graduate at UWO, University of California and McMaster University. Dr. Nisker is currently the coordinator of bioethics, spirituality and cultural issues in the faculty of Medicine and Dentistry at UWO. His current national positions include chair of the Ethics Committee of the Society of Obstetricians and Gynaecologists of Canada, Canadian Bioethics Society Council member, and Health Canada's Advisory Committee on Reproductive and Genetic technologies. Dr. Nisker has made other national and international contributions such as on the Health Canada Advisory Committee on Embryo Research and as national director of the Society of Obstetrics and Gynaecologists of Canada (SOGC), and was an author of the International Federation of Fertility Society's "Ethical Guidelines". Dr. Nisker is also actively involved on the new London Health Sciences Centre (LHSC) Patient Care Steering Committee.

Dr. Nisker has written numerous articles and book chapters on scientific and ethical issues. He has also written six plays covering issues from woman abuse to HIV to moral decision development. He has also written many short stories and poems to encourage compassionate health care. His play, "Doctor's Call" has been performed in Victoria, Vancouver, London, Toronto, Halifax, New Hampshire and Nashville. In 1996 Dr. Nisker received the Douglas Bocking Award presented to the UWO "member of faculty who, in the opinion of medical students has made the most outstanding contribution to their medical education during the previous four years".

RESEARCH IN REPRODUCTIVE TECHNOLOGY

In the words of CBC's Peter Gzowski, Dr. Nisker was a groundbreaking cancer and reproductive technology researcher when five years ago, an ethical crisis prompted him to give up his research. Since then, Dr. Nisker changed his focus to teaching medical students and doctors about ethics.

Dr. Nisker: I had been exposed as a resident in Obstetrics and Gynaecology to what are called "mid-trimester terminations", where women who are carrying a gene for what they feel, or for what society feels, is an abnormal condition, go through labor about halfway through their pregnancy as part of their termination process. It's absolutely horrible. Chemicals are injected into the amniotic fluid to terminate the pregnancy, and other drugs are given to induce uterine contractions. Sometimes the fetus comes out alive, and it is a horrible experience. So, it seemed logical that we could use the technology that we were developing in our In Vitro Fertilization program to be able to make these diagnoses earlier so the women would never have to go through this process. We would just not put in the embryos that were affected with Tay-Sach's syndrome, for example. We'd

been experimenting in mice and abnormal multi-pronucleate human embryos for years to get us to this stage. These are not human embryos, because they only consist of several cells and we didn't want to experiment with human embryos, since they can't give consent and we didn't want to get into that. This whole process is called "Preimplantation Genetic Diagnosis".

When we were doing this research, we were highly criticized by the Canadian Feminist movement, which was a very helpful and positive watchdog. They said that I was being naive, and that although I thought this research that we were doing at LHSC was for the good, a lot of people were going to take the research and use it for cloning and mass-producing human beings. As it turned out, they were right.

At the time, the only centers doing this type of research were the Hammersmith Hospital in London, England and ourselves at LHSC at UWO. Now, this is being done in at least 20 centres all over the world, mostly in the US. Where we got into a problem was when the technology that we were developing was used by scientists at George Washington University, and they did their famous cloning experiment. They were taking eight-cell embryos and making eight potential human beings out of them. That was where the Canadian Feminist movement said, I told you so, you can't do technology in a void. That was when it hit me that we had this technology and we were seeing what we could do with it instead of letting society tell science what they wanted us to investigate. As the Canadian Feminist movement was clear in saying, technology would then shape society instead of society shaping technology. I believe that this was prophetic, that I was naive and that we are now moving down those lines.

The problem is more than just cloning, it's the idea of a perfect society. It's the concept of what you would do genetic testing for. I could buy into doing this for Tay-Sachs disease, where there's very little quality of life, but would we do it for baldness? Would we do it with obesity? Where is it going to stop? Recently I read a piece in a magazine about how an American company went into Iceland, which is a small gene pool and a place where there's only a quarter of a million people. They were looking into taking genes from Icelanders and making a race of blond-haired, blue-eyed, long-legged women, which would be commercially available. It's that type of situation which really scares me, and that caused me to give up my research and spend the past five years of my life writing plays and addressing the moral issues that are involved.[1]

ON CANCER RESEARCH

Initially, the topic that had spurred Dr. Nisker to become active as a researcher was the effect of hormones on cancer. In this area, the research he carried out contributed to significantly improving the state of knowledge on this important issue.

Dr. Nisker: I come from a family where women don't live past the age of 50 because they all die of breast cancer. So I was trying to find a cure for cancer. We thought that we had a way that we could detect breast cancer through hormones, and prevent breast cancer through hormones, but we did not. Instead we found a way to prevent endometrial cancer through hormones, by giving progesterone. We did it in rabbits, since it had been found that rabbits could develop uterine cancer. Female rabbits are the only animal species that don't have estrous cycles and that don't have progesterone. A female rabbit will only ovulate during coitus. Thus, a female rabbit without access to male rabbits is in the same situation as a post-menopausal woman, in that a post-menopausal woman may still have estrogen especially if they take it in pills but their body never sees this protective hormone, progesterone, because they don't ovulate. So the rabbit was a very exact model, physiologically, for what happened. When the rabbits got cancer, I got the pathology slides, randomized them and presented them to our human pathologist who said that they looked exactly the same as human cancers. When we gave half the rabbits progesterone, the group that got the progesterone were prevented from getting endometrial cancer but the group who didn't get the progesterone still got cancer.[1]

MEDICAL ETHICS AND MEDICAL HUMANITIES

The "Yellow Brick Road" is a narrative bioethics pilot that was initiated by Dr. Nisker at the University of Western Ontario. Every other Monday evening during the fall semester, it provides thirty minutes of narrative presentation which includes original plays, adapted plays, and "readers' theater" followed by discussion of relevant ethical issues. Local and invited faculty enrich the conversation, and filming the performances for later use at Western and other universities permits future in depth digestion of issues and more personal debate.

Dr. Nisker: The program is named the Yellow Brick Road after the Wizard of Oz, because I believe that people who go into the medical professions have the brains and the heart and the courage to be the great caregivers that they want to be. Then, here we take these health care students, and we give them miles of medical ink to memorize, tons of tutored words to carry with them, and we dissolve their hearts, their brains and their courage. Especially their hearts, and this is in the name of the science of health care. Actually, I got the idea for this not from the Wizard of Oz, but from a little book by Antoine de St-Exupery called "Le Petit Prince". While reading it to my children, I noticed a gorgeous line in it that said, "It is only with the heart that thou can see correctly what is essential is invisible to the eye". That's why I feel that theater and poetry and song can touch us in the heart and can approximate empathy for a patient. We don't want to have "That's the myocardial infarction in bed 10", we want to have "That's James Jones". At Western, this concept of health care humanities will be involved in teaching bioethics with soul in medical school, and will also encompass spirituality, alternative medicine, history of medicine, and what we can learn from the evolution of medicine over the years.[1]

ON WOMEN'S HEALTH ISSUES

Dr. Nisker: I think that women's health is a huge issue, and as someone who takes care of the health of women I believe it's extremely important for these issues to be brought forward. There are so many of them... For example, women and men are not the same. They have different health needs and different expectations, and they become ill differently. Thus the prevention of illness is quite different in women. Yet, most of the research that comes out has been done in men, and it makes quite a difference in terms of the technology. For example, in Canada it is extremely difficult to get a vaginal ultrasound probe that's designed specifically for women. The one that exists is basically a modified version of a rectal probe for men, and it's used in clinics across Canada. I think that it's a cruel instrument, and we've refused to use it. We used a specific vaginal probe that was invented in Sweden but that was extremely difficult to repair once it breaks. I would have preferred that someone design an appropriate vaginal ultrasound for women rather than having to adapt one. That's just one example of how we need to be cognizant of the fact that women's health is different than men's.

The issue of genetic testing for cancer, and more specifically breast cancer, is also important. This is something that's not covered under our health care system. There are women who have a family history of breast cancer which is perhaps not strong enough to qualify them as participants in studies where genetic testing for breast cancer is done. But to them, it was extremely traumatic to watch their mother or aunt die of breast cancer. While that may not qualify them to be part of a study, I think that funding should exist for a woman to be able to be tested for the BRCA1 gene if she wishes. Many women may choose not to be tested, but right now they don't have that choice. Wealthy women can go to the US to be tested but poor women can't do that and I think that all women should have the same choices. Many women with a family history of breast cancer come to me with this question, because they're considering going on Hormone Replacement Therapy. If they're carrying the gene, they don't want to go on HRT, but if they're not carrying it they do want to go on it because they're having hot flushes. Unfortunately I can't access that information to help them choose, and that's an example of how women aren't able to make choices because of a lack of information.

I think another issue that's important right now in women's health, if I take off my hat as a clinician and put on my hat as an ethicist, is that the pregnant woman is becoming a moral battleground. The case of Mrs. G., the native woman in Manitoba who was arrested because of her solvent addiction, has really shown the moral issues that we're grappling with right now in Canadian society, such as the rights of the fetus and the right to compulsory medical care. I think that we have to be doing these moral explorations in advance of pregnant women getting into those types of situations. I chair the Society of Obstetricians and Gynaecologists' ethics committee and we try to stay ahead of these questions but it's very difficult. In reproductive medicine, there's a tremendous amount of issues and there are many complex situations that women can be put into.

In general, prevention is a very important part of women's health, and one area that's important with respect to prevention is sexually transmitted diseases. In the age of the birth control pill, condoms are used less and probably with less proficiency than previously. It is difficult for young women to ask their partner to use condoms when he knows that she is on the pill. When a young woman asks her partner to use a condom, she feels that she is risking the relationship and will often chance that he is not carrying HIV/gonorrhea/herpes or any other potentially harmful organism rather than risk the relationship. We must educate on this issue, even starting in primary schools, to explain that if you care for someone you must protect them, and that includes using barrier methods even if pregnancy is prevented through the birth control pill. I think that sexual education programs run by health care students in high schools are extremely valuable, both for the high school students and the health care students. This way, health care students learn the importance of prevention and gain the interpersonal skills that will make them more communicative caregivers in the future.

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ETHICS

EDITOR: DAVID J. SATIN

AN EDITORIAL: FEMALE GENITAL MUTILATION AND CULTURAL RELATIVISM

By David J. Satin, MEDS 2001

As the Ethics Editor, I have chosen to write an editorial on a subject raised by an interesting paper which appears elsewhere in this issue entitled, "Female Circumcision or Genital Mutilation: a Rational Approach", written by Reena Bhargava & Lubna Tirmizi. I employ female genital mutilation as an example of the interface between Cultural Relativism and 'Women's Issues' at large.

It is often difficult to question the ethical legitimacy of harmful norms around us, for it is usually only violations of norms, rather than norms themselves, that draw that kind of attention. At the crossroads of such fields as political science, anthropology, sociology, and ethics lies a debate over Cultural Relativism. As its name suggests, in a moral context this doctrine implies that "the moral code of a society determines what is right within that society, and it is mere arrogance for us to try to judge the conduct of other peoples."[1] Evidence often cited in support of Cultural Relativism includes the disparity of ethical judgements about various acts throughout the many cultures of the world. Cultural Relativism has in turn been used as an ethical defense for many of these acts, among them the practice of female genital mutilation (FGM).[2]

To better understand the overall strategy of this work, that is analysing and relating *token* phenomena such as FGM to *types* supported by Cultural Relativism, consider the following analogy: From a valley, many rivers may seem unconnected, yet upon ascending a mountain these same rivers can be seen as parts of a network. Similarly a number of physical phenomena such as planetary motion and pendulum clocks conceived of as unconnected on a practical level become one in the same phenomenon in the context of Universal Gravitation. So too, practical ethical debates over FGM, foot-binding, and augmentation mammoplasty may be seen as special cases of a greater debate over the types of support derivable from Cultural Relativism.

Just as climbing the mountain might help us plan a system of dams, ascending to a metatheoretical[3] level may provide the necessary perspective for one to more easily locate, among a general class of cultural practices, the ethical content of one's own. Lastly, considering how no physical change can be effected from a mountaintop, it is essential to return to the valley floor to begin construction. So it will be important to return to the practical ethical forum of our cultural practices with the insight derived from high atop our metaethical mountain.

ANALYSIS

"It's how things are"

One might argue that FGM is morally permissible solely on the grounds that it is embedded within many cultures - that is, in virtue of its entrenchment in the mores of its practitioners/recipients and its virtually unanimous acceptance as a way of life.[4] This argument is grounded in the general principle that social acceptability determines morality (i.e. mores = morals). Let us examine how consistent this principle is with our intuitions. Slavery was a public way of life for many of our ancestors from biblical times, through antiquity, well into the twentieth century.[5] I suspect that few would assert that slavery is morally good (or neutral) in virtue of its public and widespread practice. Now, if such a temporally and geographically popular practice as slavery cannot gain moral support from its cultural entrenchment, surely FGM cannot expect such similar support. But the Cultural Relativist is not yet forced to retract on this account, for she may still point out the temporal disanalogy between FGM and slavery.

The Cultural Relativist and proponent of FGM may argue that slavery is no longer a publicly supported practice while, in many places, FGM certainly is. Therefore, it is open to this proponent to claim that a given practice may be justified for the period of time in which that practice is publicly condoned and commonly performed. That is, unlike slavery, FGM is morally permissible because it is presently entrenched within many cultures. Let us examine the implications of such a principle. If we grant that a practice is morally permissible because it is presently accepted within a culture, then we must also grant that slavery *was* morally permissible in early twentieth century America. Similarly, we must accept that Apartheid was a just policy in the South Africa of the nineteen-eighties, and if you happened to be living in WWII Berlin you would be mistaken in asserting that Nazism is wrong. Furthermore, in granting the Cultural Relativist's updated principle we must accept that whatever practices are currently entrenched is how things ought to be... at very best, an uncomfortable position indeed. If one wishes to justify FGM on cultural grounds, one had better have more of a story to tell - and the Cultural Relativist certainly may.

"It works for us"

The Cultural Relativist and proponent of FGM might argue that perhaps certain cultural practices have powerful functional roles in societies. This functional role may be cashed out in two ways—physiologically and psychologically. What I call the physiological role aims to justify FGM on the grounds that it has an overall physiological benefit for the population (e.g. lower incidence of STDs). As the physiological 'success' of a given practice is largely a contingent fact, I will grant the possibility of a society in which, through some mechanism unknown to me, FGM results in a net physiological benefit to the overall population. I therefore offer the following, standard, 'in principle' counter-argument to the intuitive defensibility of such an attractive social arrangement.

The structure of this hypothetical physiological argument is as follows: practice X, which is harmful to a given segment φ of population Γ, ultimately results in greater physiological health for population Γ, thereby justifying practice X.[6] This argument is grounded in a naïve utilitarian principle that achieving 'the greatest good for the greatest number' justifies acts which, in themselves, harm individuals. Consider H.J.McCloskey's 1965 counter-example, highlighting the injustice inherent to a practice which harms individuals for the purpose of the good of society:

> Suppose a utilitarian were visiting an area in which there was racial strife, and that, during his visit, a Negro rapes a white woman, and that race riots occur as a result of the crime, white mobs, with the connivance of the police, bashing and killing Negroes, etc. Suppose too that our utilitarian is in the area of the crime when it is committed such that his testimony would bring about the conviction of a particular Negro. If he knows that a quick arrest will stop the riots and lynchings, surely, as a utilitarian, he must conclude that he has a duty to bear false witness in order to bring about the punishment of an innocent person.[7]

If one is swayed by the intuition that it would be unjust to harm an innocent individual for the good a larger group, then one cannot employ the physiological argument in defense of social practices that are harmful to a segment of the population—lest one sanction injustices.

The second role, the psychological role, can be presented as justification for practices like FGM on the grounds that the population gains psychological comfort, stability, and a sense of identity through the maintenance of culture. This argument, potentially confused with the next argument, falls prey to the same counter-argument as the physiological argument.

"Every thing has a right to self-preservation"

Justification via a 'social argument' is practically orthogonal to the 'psychological argument'. One might argue the very existence of a given society is dependent upon its particular set of practices. The continuity of cultural practices is, ipso facto, a constitutive property of a society.[8] A 'social argument' in support of integral cultural practices (harmful or not) can be extracted from the judgement Lord Nelson rendered at the infamous British criminal case of R. V. Brown.[9] As part of his judgement Lord Nelson constructed the following analogy, essentially outlining the 'social argument': A society, like an individual, has the right to defend itself against danger. Just as societies typically reserve their highest penalty for treason so as to insulate themselves from foreign attack, so too must a society defend against attack from within. Manipulation of integral cultural practices constitutes a form of treason, for the alteration of these specific practices effectively destroys the old society, replacing it with a new one. Just as an invasion of Britain by France would bring an end to 'British society', replacement of typically British practices by 'Neo-British' practices would bring about a similar 'social extinction'.

A Cultural Relativist and proponent of FGM may employ this argument to say that FGM is just such an integral part of many of the cultures in which it is practiced. Furthermore, since each culture has a right to protect itself to ensure its survival, maintenance of its integral practices, including FGM, is a right. To answer the challenge of the 'social argument' we must once again return to the slavery analogy. Slavery was an integral part of many cultures, including North American. Today we look upon slavery unfavorably and openly express approval at this change of sociocultural practice. Societies are composed of individuals, and just as individuals can commit injustices, so too can societies.

Societies are dynamic entities. Today's Canadian society is markedly different from that of one hundred years ago, yet would any of us liken this transformation to treason? Who among us views our great innovators of art and science as public enemies? Changes in sociocultural practices can be beneficial or detrimental to a population. There is no reason to believe that the most static society ought to be the most ethical. Societies are composed of people and it is people that have rights - not practices. People have the right to stay the same and people have the right to change. The choice to exercise one's rights will be the focus of the final culturally relativistic argument we will consider.

"But we choose it"

The Cultural Relativist and proponent of FGM may argue that respect for choice distinguishes practices like FGM from those like slavery and that by *choosing* a harmful practice one effectively justifies the practice. The Cultural Relativist might phrase the argument as follows: An individual may freely choose X, and just because X reflects a preference for their culture (not yours) doesn't allow you to say that they shouldn't choose X. I will once again grant the proponent of FGM the strongest possible case. That is, a situation in which a woman, old enough to make an informed choice, chooses FGM and quite happily celebrates her culture through practice. The proponent of FGM may now ask what could be unethical about such a scenario.

To properly address this argument we must first ask ourselves what could motivate a person to choose to

undergo such a harmful procedure. The answer, in this scenario, clearly reads that she does so as a "celebration of her culture through practice". Before responding to this answer, let us consider analogous practices from other cultures. For a millenium, many Chinese women 'chose' to bind their feet, enduring pain and incapacitation in the name of fulfilling their cultural heritage. Eighteenth century English women 'chose' to wear tight corsets, restricting a range of physiological functions and inducing bouts of fainting, for that was their culture.[10] These practices have several things in common with FGM. Most saliently however, is the way in which each is a 'chosen' practice, yet the social penalty for choosing to forego the practice is typically heavy indeed.

Nonconformity is frowned upon in most societies and the coercive force of one's society is often unparalleled in one's experience. Coercion can be a subtle process, especially when it is endemic. This may help explain why it is so easy to see the harmful practices of other societies, yet so difficult to note them in our own. In many societies, 'choosing' to forego a social practice carries stigma, thereby decreasing one's ability to succeed within those societies. We can imagine how an English woman's choice to forego a corset would certainly have lowered her social status, thereby diminishing her chances of marrying successfully, bearing children, and establishing the kind of life many expect. The basic drive for social acceptance and procreative opportunity may certainly constitute ample motivation for conformity.

Returning now to our woman's choice to undergo FGM, we must ask if the conditions for an *uncoerced*, informed choice are present. Would she choose FGM were there no social penalties associated with foregoing the procedure? Would she prefer a society in which she could celebrate the non-harmful aspects of her culture? Recall that our analogous Chinese and English women, immersed within their culture, may have been looking forward to their respective practices since childhood. We can however, imagine how these physically harmful practices come to be identified with the social successes they entail.

From the many judgements of the R V. Brown case alluded to earlier, comes the principle that there are criminal acts that cannot be decriminalized by consent (e.g. irrespective of consent, it is illegal to duel to death or dismemberment).[11] So it is, I propose, with the morality of harmful acts which cannot practically be chosen freely (i.e. free of coercion). The Cultural Relativist may argue that each culture provides its own unique brand of pressure and no choice made within the context of a society can truly be free from the coercive force of that society. Few would debate this virtual tautology. Nevertheless, when a society places a segment of its population in a position where they must make a choice regarding a personally harmful practice, of which the sole justification *is the choosing* of that practice for sociocultural benefit, the tight circularity of justification renders the entire system suspect. We are thus lead to ask, "Why must a segment of a population suffer harm for a sociocultural benefit enjoyed by all?"

It seems as though there might be an inequality of sorts built into the system. There may, however, exist a society in which all segments of its population make similar uncoerced, informed sacrifices for the sociocultural benefit of all.[12] While it would thus seem that there is a logical space in which practices such as FGM may be justified on culturally relativistic grounds, one must eventually descend from the metaethical mountaintop and ask if such a hypothetical society actually exists. While the actual existence of this hypothetical society seems at best implausible, I must defer such research to anthropologists.

COMPLEMENTARY CONSIDERATIONS

As I've alluded to earlier, while our intuitions may speak to us strongly about practices from which we are far removed, (e.g. slavery, Apartheid, Nazism, foot-binding, and corsets) it is the practices which surround us that we are least likely to question. Having pitted (what I hope has been) a complete set of culturally relativistic defences for FGM against the aforementioned counterexamples, one might just as well substitute a number of North American practices for FGM. Prescinding from matters of degree, if North American readers were under the impression that FGM is the *kind* of practice that could never happen here, perhaps we ought to reconsider.

In order to uncover some North American candidates for "harmful practices, the sole justification of which is sociocultural", one need only ask members of another society.[13] They might suggest that we address, as seriously as FGM, the following questions: Considering the immensely coercive force of the North American media and our social infatuation with a given body image, how might we justify the prevalence of cosmetic breast implants for the otherwise healthy woman? How can we explain the prevalence of such an immediately painful and eventually harmful practice as bulimia? From the mountaintop, one might group these phenomena under the heading of 'harmful practices which improve social standing'. Subjecting one's own practices to scrutiny comparable to that of FGM may indeed allow for a more introspective approach to not only FGM, but to one's own values as well.

CONCLUSION

Cultural Relativism is defensible insomuch as Ethical Subjectivism is. There is nothing to stop a person from valuing inequality, oppression, or slavery. However, within this work I have argued that if one's core values include equality and fairness, then barring the aforementioned hypothetical society, one cannot defend practices like FGM through Cultural Relativity. I have grounded these arguments in intuition through analogy and in principle via analyticity. I began by noting that it is often difficult to question harmful norms that surround us. Perhaps even more difficult for physicians, is returning from the mountaintop to act in accordance with one's beliefs, especially when they are contrary to social norms. Mohandas Gandhi proclaimed, "In matter of conscience, the law of the majority has no place."[14] There may be no place where such wisdom is more applicable.

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3. 'Metatheory' refers to theory about the nature of a given discipline, or 'theories about theories', for short. (Metaphysics = Discourse about the nature of physical theories, Metaethics = Discourse about the nature of ethical theories)
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MEDICINE ON THE INTERNET

EDITORS: ANAND PANDYA & MUNSIF BHIMANI

A LOOK AT WOMEN'S HEALTH ON THE INTERNET:

By Rupinder Singh Sahsi, MEDS 2001

There are a number of excellent resources on the World Wide Web related to the topic of Women's Health. By no means can a single article capture the vast amount of information that is available at a few clicks of the mouse button. From the riches of the Internet, I offer the following selections for your perusal.

Women's Health Interactive (WHI)
http://www.womens-health.com/

This site provides comprehensive resources for patients and health professionals alike. Of note are the WHI Health Centers that are designed to facilitate patient education on issues like gynecology, cardiac health, infertility, (peri) menopause, and nutrition. As well, web surfers can tap into WHI's list of current consumer research studies, indices of women's service providers, and on-line discussion forums. This award-winning site strives to be "an unique and interactive learning environment where women gain knowledge and mastery of their health through the multidisciplinary resources." Definitely worth checking out and potentially a useful site to refer to your more net-savvy patients.

Women's Health & Medical Info
http://www.cbull.com/health.htm

It is not exactly Yahoo!, but this site delivers 85+ kilobytes of links on online women's resources "for your mental and physical health and well being." This site was created after over a year of searching for women's health and medical sites on the Internet. There is nothing fancy here, but a straightforward alphabetized list of links to medical sites that might even be slightly related to women's health. This site is an offshoot of the "Best Sites For Women" web site (http://www.cbull.com) authored by Claire Bull. Be warned that there is a lot of content here, so if you're looking for something specific in a hurry, this might not be the best place to start.

The American Medical Women's Association
http://www.amwa-doc.org/

The American Medical Women's Association is an organization of over 10,000 female physicians and medical students "dedicated to the care of the woman patient and serving as the unique voice for women's health." This web site focuses mainly on the AMWA itself - annual meetings, committees, programs, projects, etc. However, if you're looking for information on health topics, scroll down the main page to the little graphic of the red cross. It links you to a series of online documents geared towards educating the public. Although they are well laid out, the graphics are nothing to get excited about. I found some of the documents a little simplistic, but very effective at conveying the key messages that are fundamental for patients.

Medscape Women's Health
http://WomensHealth.medscape.com/Home/Topics/WomensHealth/WomensHealth.html

I was first introduced to Medscape (http://www.medscape.com/) a while ago through the advice of a colleague, and I've been hooked ever since. From the makers of what is probably the #1 medical site on the Internet, this page does not disappoint. While many sites on the topic of Women's Health have a greater patient-education focus, Medscape's page delivers the information physicians are looking for. New articles relevant to areas of women's health are posted daily with access to full-text journal sources. In addition, there are case challenges, clinical quiz questions, and the "virtual consult" where peculiar but interesting cases are laid out by the experts.

JAMA Women's Health Information Center
http://www.ama-assn.org/special/womh/womh.html

This is another excellent resource for physicians and health professionals looking for recent and accurate information. The clear and simplified layout lets this page load up lighting-fast, and enables you navigate the site with ease. The Newsline gives you updates from Reuters Health, special in-depth articles from major professional sources, and coverage of key conferences from around the world. Regularly posted Journal Scans keep tabs on women's health articles that appeared in the literature, presenting abstracts organized by categories including adolescent health, breast cancer, menstrual cycle, and recurrent pregnancy loss to name a few. Full text articles from AMA scientific journals are also available, potentially saving one the bother of a full subscription. Also of note are the STD and Contraception Information centers. Don't let the initially spartan appearance of this site fool you, there is a lot of information available once you make just a few simple clicks.

And finally...

When dealing with sensitive issues related to Women's Health, health care professionals have to be alert that increasing proportions of their patient population will be referring to sites such as these prior seeking medical advice. Many even prefer the autonomy and self-reliance of being able to access such information on their own time. It is helpful to keep an eye out for what information (and misinformation) is floating around the information superhighway, so that one can help direct patients to authoritative sources. Furthermore, letting patients do their own reading on the Internet is not only better for their ability to process information at their own pace, but will likely help to decongest some of the busy schedules practitioners face everyday.

As always, the sites mentioned in this article, and others on the subject, can be found in the Medical Links database of the Meds2001 Web Site (**http://meds2001.garage.org/**), under the "Women's Health" subject heading. Ω

INFERTILITY TREATMENTS AND WOMEN'S HEALTH

By Najib Safieddine, MEDS 2001 & Mahmoud Sharaf, MEDS 2002

INTRODUCTION

The last decade has seen a rapid increase in the number of techniques and treatments available to non-fertile couples for having children. Unfortunately, and perhaps quite predictably, legislation has not kept pace with medical science. Canadian family law finds itself in a situation of great delicacy as it searches for guidelines that will prevent the litigation nightmares now common in the United States. However, just as important as the custodial issue is the item of women's health.

THE ROYAL COMMISSION ON NEW REPRODUCTIVE TECHNOLOGIES

The *Royal Commission on New Reproductive Technologies* (1993) issued a final report that proposed several recommendations to standardize and simplify Canadian law on assisted conceptions. Some of the proposals included:

1. That the donor's rights and responsibilities of parenthood are severed by the act of sperm donation;
2. That the male partner of the donor insemination recipient, if he has given his written consent at the time of insemination, be considered the legal father of the child;
3. That the married or cohabiting male partner should only be able to disavow paternity if he did not consent in writing to the insemination; or he did not enter into a parental relationship with the child knowing he was not the genetic father; if he had acted as a father to the child only because he believed he was the genetic father of the child;
4. That if the legal mother of the child has no male partner, the child has the legal status of "father unknown";

While providing valid recommendations pertaining to legal custodial issues, the Royal Commission has not fully addressed the implications of infertility treatments on women's health.[1] This comes despite critical input provided by the Canadian Advisory Council on the Status of Women in their brief to the Commission.[2] Specifically, ovarian induction is an infertility treatment that constitutes a possible health risk that was not seized upon by the Commission.

HEALTH RISKS

Many women faced with infertility are treated with ovulation inducing medicines. However, evidence has raised concerns about the possible risk of ovarian cancer.[3,4] Agents such as human menopausal gonadotropin (hMG), follicle stimulating hormone (FSH), and FSH analogues are not without certain "toxic" consequences. Ovulation induction can lead not only to higher incidence of spontaneous abortions, but also to diseases such as ovarian hyperstimulation syndrome (OHSS) which results in the secretion of supraphysiological levels of estradiol and severe health complications, possibly requiring hospitalization.[5] Ovulation stimulation drugs have been associated with hot flashes, multiple gestations, visual disturbances, and cervical mucous abnormalities. Thromboembolic disease is also suspected to arise from OHSS.[6] Evidence suggests that such treatments affect the proliferation of epithelial breast cells and thus add to the risk of breast cancer.[7]

Although some of these risks have not yet been absolutely confirmed to be the sole and direct result of infertility treatment, and research is still underway, the possible risks are too grave to ignore. This necessitates the intervention of the legal system to address the issue immediately.

CONCLUSION

In the past, the *Food and Drug Act* has empowered the federal government to intervene in blocking potentially risky drugs and therapies from being used in Canada until properly studied and validated. It is necessary for Canada to uphold its strict tradition of rigorous evaluation of new drugs and therapies, particularly when it comes to reproductive health. The Canadian courts and the public have shown a firm expectation that government and business must not only prevent clear obstacles to national health and safety but also anticipate them. In *Hollis v. Dow Corning*, a case of silicone breast implant liability, the Supreme Court confirmed legal responsibility of the manufacturer despite little evidence at the time of the inherent danger. In New Brunswick, the provincial government was held liable for the adverse effects of DDT pesticide use after the fact despite no convincing evidence at the time. The ethical-legal principle of government exercising due care for the health of the population at the stage when treatments are only potentially problematic should be appealed to. The urge to provide the choice to infertile women to have children if they so desire can only be outweighed by concern for their health and safety.

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Ω

WOMEN & INFERTILITY: A HISTORICAL PERSPECTIVE

By Kent Dunn, MEDS 2001

Is infertility on the rise because women are delaying childbearing in pursuit of career success? Does it affect white women more than African-American women, or the rich more than the poor? Has infertility reached epidemic proportions among the educated and affluent? Most would answer yes to these questions—and most would be wrong.

The erroneous idea that current infertility rates reflect a new phenomenon in North American society provides a distorted image of the present and obscures the relationships between contemporary ways of coping with involuntary childlessness and those of past generations. For example, in the seventeenth century few women would have considered seeking medical advice as infertility tended to be viewed as the will of the Lord or the work of the Devil.[2] By the late nineteenth century, physicians were performing surgery, such as ovarian transplantation, in an attempt to restore fertility.[2] The late twentieth century has seen the development of *in vitro* and related reproductive technologies that have increasingly severed reproduction from sexuality. Thus, throughout the last three centuries, the inability to procreate has been medicalized—converted from a socio -religious state into a medical condition.

In addition, the approach to infertility, whether historical or contemporary, accommodates a persistent gender bias: the tendency to view women's bodies as inviting intervention and men's as demanding caution. This bias is manifest in relation to the form of medical investigations and infertility therapy, and in the enthusiasm and frequency with which they are performed. This is exemplified by the fact that historically many fertile women have been subjected to invasive, often dangerous procedures, in order to enhance the capabilities of a partner's weakly motile sperm.

Such relationships will be explored by examining the ways in which the inability to conceive has been treated by medical practitioners, perceived by society, and experienced by individuals from the 17th through to 20th century.

From the 17th to the early 19th century, popular and medical opinion alike held that female sexual pleasure was almost always essential for pregnancy to occur.[1,3] According to Etmuller the "languishing" of a woman's "venereal appetite" often caused barrenness.[1,3] Mauriceau went so far as to cite "the insensibility of some women, who take no pleasure in the venereal act as the most frequent reason why this orifice opens not in this act to receive the man's seed".[3] Men on the other hand were only held accountable if they were impotent or in some way "unable to perform their marital duties".[2]

Therefore, barrenness was a woman's problem, and self-treatment was the usual means employed to alleviate it. American women kept medicinal recipe books which often contained specific preparations to treat various menstrual irregularities that were believed to cause barrenness and that could also be used for the prevention of miscarriage. If self-treatment failed, a woman might have consulted a midwife, who would have prescribed various botanical preparations.[1,2]

The first steps towards the medicalization of infertility began with James Graham (1745-1794). Graham, something of a maverick, built a fortune with his ingenious linkage of sexual pleasure to electrotherapy in order to cure sterility.[4] On his return to Great Britain in the late 18th century he constructed the "Temple of Health" in London. Here an audience of men was seated in chairs that provided mild electrical shocks (coined "magnetic thrones") while listening to Graham lecture on potency. Women who came to the temple heard lectures on fertility given by a member of their own sex.[4] The well to do had a further option - Graham's vibrating "celestial bed". The "superior ecstasy which the parties enjoy in the Celestial Bed", promised Graham, was "really astonishing...the barren certainly must become fruitful when they are so powerfully agitated in the delights of love".[4] The bulk of his audience, no doubt, came to the Temple to be titillated by the mild electrical shocks or by the lectures themselves. In fact, it was hard for his contemporaries, as it has been for generations since then, to take Graham seriously.[4]

In the 1860's and 1870's technological developments in the form of new instruments and surgical techniques burst onto the medical scene, thus providing new opportunities for seeing, and for reconfiguring the interior of women's bodies.[2,5] The use of instrumentation and surgery on women's sexual organs became commonplace by the end of this period, especially among physicians eager to establish themselves as "experts" in an emerging medical field. Women themselves, apparently in increasing numbers, actively sought surgical treatment, both demonstrating the existence of demand for these methods and encouraging more physicians to provide them.[2] The "women's surgeons" of the 1850's and 60's, and the women who patronised them, had a profound impact on what would become the specialty of gynaecology.

In terms of the history of infertility, two of the most important "women's surgeons" were J. Marion Sims and his assistant Thomas Addis Emmett. Both worked at the Woman's Hospital in New York - the first hospital devoted exclusively to the surgical treatment of disorders of women's reproductive systems.[2] Sims felt that the overwhelming majority of the diseases of the female reproductive system were structural, and therefore curable by surgery. Believing that most dysmenorrhoea and sterility resulted from a mechanical blockage of the cervix,

Sims thus reasoned that surgery to widen the cervical opening should alleviate pain and allow conception. Sims and Emmett performed countless "cervical incisions" in order to make its opening into the vagina larger.[2] However, Sims did not consider pregnancy a measure of success; rather, women were "cured" if the os was opened, the cervical canal straightened, and any of the infections that the surgery itself often generated, were alleviated.[2] In fact, Marsh and Ronner's historical analysis of Sim's records revealed that some women received surgical interventions even when they had no obvious symptoms that might account for their sterility. Marsh and Ronner concluded that much of Sims' surgery for infertility was performed to 'correct' what seems to have been normal organs.[2] However, Sims did succeed in revolutionising medical ideas about infertility, and in the process ushered in a wave of technological innovation that contributed to the rapid emergence of the field of gynaecology.

A number of societal trends following the Civil War resulted in a decreased birth rate, and as more women pursued higher education and careers, the people's views on the aetiology of sterility centred on women's 'inappropriate' behaviour.[2,5] Harvard physician Edward H. Clarke's 1873 "Sex in Education" argued that young women were educating themselves into sterility. He believed that young women should not be putting in long hours of studying difficult academic subjects, but should instead learn slowly and completely, and rest their minds during their menstrual periods. Education, he stated, had a "sterilizing influence" on young women and in another generation, "the race will be propagated from its inferior classes".[6]

By the end of the century, new ideas and evidence began to suggest that infertility, rather than resulting from women's refusal to bow to conventional behaviour, could be accounted for by more specific physiological disorders, particularly of the ovaries and fallopian tubes. Perhaps the most important single factor in accomplishing this change was the dramatic alteration of medical views of gonorrhea.[2] As practitioners began to accept gonorrhoea as a cause of sterility, they were forced to give more attention to the existence of infertility in males. By the end of the century, the idea of semen examination took hold among a number of the field's prominent practitioners (although it did not become a routine part of arriving at a diagnosis of infertility until the 1950's).[2] The realisation that men could be sterile marked an important shift in attitudes among gynaecologists.[8]

The discovery of estrogen in 1923 and progesterone in 1929, coupled with the newly discovered intricacies of ovulation and implantation, marked the beginning of a journey that led to the creation of the birth control pill, the infertility drugs pergonal and clomid, and successful in vitro fertilization.[5] Fertility (and infertility) in women could now be understood and, in some cases, treated.

The period from the 1960's to 80's illustrates some new dimensions of some aspects of infertility. After 1965, birth rates would begin to plunge and larger numbers of couples would choose to be childless; at the same time, dramatic advances would occur in the ability to treat infertility effectively.[2] Attitudes towards the infertile were also changing as antinatalist sentiments challenged the pronatalist consensus that had held sway among the post-war generation. Instead of sympathy, in the 1970's women feeling anguish over their inability to have a baby might be reminded that pregnancy was unattractive or that the world was overpopulated anyway.[2,9] Such opinions did not, of course, diminish the desires of the involuntarily childless. And despite fears held by advocates of the 'traditional' family, a feminist movement that enabled more women to attend university and succeed in careers did not inevitably create a generation of women antithetical to motherhood.[2]

This change in attitude is perhaps best illustrated using in vitro fertilization as an example: what was heralded to be a technological miracle in the 40's, was a morally questionable endeavour in the 60's and had become a veritable political minefield by the 70's.[7] In fact, by the mid 70's the Right to Life movement had succeeded in shutting down American IVF experimentation.[2] However, work continued in England where Cambridge University physiologist Robert Edwards and gynaecologist Patrick Steptoe performed at least 80 in vitro fertilizations before they effected the first successful implantation,[2] thus heralding the ultimate separation of the sexual and reproductive acts. The first test-tube baby, Louise Brown, was born on July 25, 1978 in Bristol, England.[2]

Present day technologies such as achieving pregnancy post-menopausally, the possibility of harvesting and freezing sperm post-mortem, and breaking the genetic tie between mother and child through the use of donor eggs, are among the practices that have made IVF controversial. In addition, the daunting prospect of cloning babies is now more than ever a possibility. Such new techniques have further subverted the link between sex and reproduction and challenged traditional verities. One must remember that the desire to use these techniques, like those employed in the past to assist infertile women to conceive, is socially and culturally conditioned. Employing a historical perspective contributes to one's understanding and evaluation of the assumptions about the roles of reproductive technology that underlie the controversy over its use.

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Ω

UNWINDING THE SNAKES: REDISCOVERING THE TRUE SYMBOL OF MEDICINE

By Samir K. Sinha, MEDS 2002

While medicine has been associated with serpent symbolism since humanity began recording the art, most authorities agree that the Aesculapian staff is the true symbol of medicine. Although seen frequently, few people are aware of its historical origins, and its relation to the profession. If the Aesculapian staff (around which one serpent) is entwined is the correct symbol, why then is the caduceus of Hermes (around which two serpents are entwined), so frequently adopted as the symbol of medicine? And is the caduceus an appropriate symbol for the medical profession? This paper will explore these questions.

AESCULAPIUS AND HIS STAFF

Homer, in the *Illiad*, mentions Aesculapius only as a skilful physician; in later times, however, he was honored as a hero and eventually worshipped as a god. The first mention of Aesculapius occurred in a Greek inscription recording the establishment of an Aesculapian shrine in Athens in 420 BC. Aesculapius was the son of Apollo, the primary god of healing in the Greek pantheon, and the maiden Coronis. During his lifetime, Apollo passed along his knowledge of medicine to Chiron, the son of Saturn. It was Chiron who later helped to raise and instruct Aesculapius in the art of healing using herbs, potions, and incantations.[1] Further to the legend, after Perseus had beheaded Medusa, Athene directed young Aesculapius to extract blood from her headless body. Blood from her left side was lethal to the touch, while blood from her right side possessed unique powers to resurrect the dead.[2] With these new therapeutic resources, Aesculapius now achieved notable clinical successes, albeit in small non-randomized control trials.

Aesculapius became so proficient in healing that he soon surpassed his master. Furthermore, his powers became so well-known that people came from all over Greece to see him. Aesculapius was frequently represented in statues standing dressed in a long cloak. His two most important attributes began appearing together towards the end of the 4th century BC in the form of the Aesculapian staff, with a single serpent coiled around it. And, unlike the caduceus, its meaning seems to have developed from a utilitarian standpoint rather than as a sign of position or authority.

The snake itself has both a practical and metaphorical meaning. The snake has always been considered sacred and worshipped for its representation of wisdom. It also came to symbolize the gods of fertility and since it could shed its skin, it was thought to possess powers that enabled it to live forever. Physicians in earlier primitive cultures thus ate snakes, believing they would become more efficient healers.[3] Aesculapius' later association with the serpent resulted from an incident that occurred while he was in the house of a patient. Tradition states that while he was deep in thought, a snake coiled itself around his staff. He killed the snake and then another one appeared with an herb leaf in its mouth and restored the dead serpent to life.[4] As a result of this incident, Aesculapius kept non-poisonous snakes in temples to help heal the sick. In addition, the species of snake found on his staff, *Elaphe longissima*, became an integral part of the temples later built in his honour. Because of its natural diet of rats, the priests used it as a biological pest control. As they became a more prominent fixture, they began to play an important part in the rituals of the temples.[5]

The staff, the other symbol associated with Aesculapius, was adopted as a symbol of sovereignty in Egyptian and Sumerian cultures. While it denoted power, the emblems attached to it were associated with the god under whose name it was cast.[6] The staff symbolized plant growth and was associated with both death and resurrection of the dead. In this regard, the staff was very much like the snake shedding its skin. Both indicated that life was everlasting. The sturdy nature of the staff may as well be seen as the traveller's staff, reminding us of the long journeys of Aesculapius from his home in northern Greece throughout the Hellenic world. It thus symbolizes the inexhaustible willingness of the physician to travel long and wearisome journeys to help the sick.[7]

Aesculapius became recognized as a god because, in ancient Greece, it was believed that anyone who recovered from an illness was regarded as being resurrected from the dead. On one occasion Aesculapius is said to have raised a man from the dead and delivered him from Hades, a privilege reserved for the gods. Because of this, Pluto accused Aesculapius of diminishing the number of souls in Hades. An enraged Zeus, fearing that Aesculapius might make all men immortal, slew him with a thunderbolt.[8] Before his death, however, Aesculapius is said to have sired six children. Two of his daughters were Hygeia and Panacea. The beautiful Hygeia was the goddess of health and preventative medicine; Panacea assisted her sister in the temple rites and tended the sacred serpents. Aesculapius' two sons, Podalirius and Machaon, were both physicians to the Greek armies besieging Troy. (Illiad II, 645-8)

The cult of Aesculapius originated in Thessaly where he was worshipped as a healing saviour, and quickly spread throughout Greece. The healing practices of Aesculapius were passed down from father to son, each generation being recognized as Asklepiads or healing priests. The name itself is interpreted to mean "healing soothingly and deferring the withering that comes with death."[9] They practiced their skills in magnificent temples,

built in honour of Aesculapius. These temples are generally acknowledged as the origins of hospitals. In these temples, wounds were dressed and sanitation and preventative medicine were practiced and taught, intertwined with religious rituals.[10] For the ancient Greeks, medicine and religion were inseparable. Over time more than 200 asclepia were built throughout Greece, the greatest at Epidaurus, where the theatre seated 20,000 persons.[11]

Obviously, Greek medicine was rooted more in mythology and theology than in science. It was remarkable that the cult of Aesculapius was popular and influential throughout Greece for about 1,000 years. In the Roman Empire, the worship of Aesculapius was bitterly attacked as Christianity gained popularity, though the cult survived until the 6th century.[12] Secular medicine also began competing with ecclesiastical medicine in Greece. In his essay The *Sacred Disease*, Hippocrates, credited with the liberation of medical ethics, attacked the theory that illness is caused by the gods, and claimed that all diseases, including epilepsy, had natural causes. Even Hippocrates, however, occasionally advised prayer as an aid.[13] The Hippocratic oath begins with the words "I swear by Apollo the physician, by Aesculapius, Hygeia and Panacea, and I take to witness all the gods, all the goddesses...", though some no longer ascribe to it.

THE CADUCEUS

The caduceus, the staff around which two serpents are entwined, ultimately came to be associated with the Greek god Hermes. Hermes was the son of Zeus and Maia, daughter of Atlas. Graceful and swift, he served as messenger to the other gods. Hermes was considered on various occasions the god of commerce and merchants, messengers, thieves and the underworld deity who conducted souls to Hades. The caduceus represents the wand of Hermes and connotes his patronage of peace, trade, commerce and communication. In the account of the origin of the caduceus, it was stated that Apollo gave his staff to Hermes as a reward for Hermes' invention of the lyre. According to Apollo, the staff had the power to unite all beings divided by hate. When Hermes travelled to Arcadia, he saw two serpents fighting. With dispatch, he threw the staff between them and they wound around it in a friendly manner.[14] Wings were later added to this emblem as a symbol of Hermes' speed and the caduceus was born. Because Hermes was the messenger of the gods, his staff, which came to symbolize authority and peace, became the herald's wand in times of war. As warring combatants might do today with a white flag as a symbol of truce, the Romans expressed their desire for negotiations with enemies under the caduceus.[15]

There are few actual references to healing functions attributed to Hermes, although he was a god of gymnastics and athletics, and was considered to be a guardian of health.[16] Hermes played some medical roles in that he did assist in conducting the dead to the underworld and also received some credit for relieving plagues and epidemics in Asia Minor. In peacetime, however, Hermes and his caduceus became primarily associated with trade and prosperity, retaining their wartime roles in negotiation and communication. Throughout Europe before the last century, the caduceus was a purely commercial symbol without medical connotation. Hermes carried over into Roman mythology as Mercury. A good deal of our English language is rooted in the commercial connotations of Hermes' function. The words "commerce," "merchant," "market," "mercenary," and "mercantile" all come from Latin merx or mercis (goods) and mercer (to traffic).

THE MIDDLE AGES AND THE ROOTS OF CONFUSION

In determining which god more accurately represents the medical profession, most scholars agree that Aesculapius wins hands down.[17] After all, he was the god of medicine, healing, and physicians. The caduceus, on the other hand, is the symbol of Hermes, who had little to do with medicine. Since the Renaissance, however, the emblem of Hermes has often been confused with the staff of Aesculapius in representing the profession. From this unrelated past, how did Hermes and medicine get to be bedfellows?

As noted, although Hermes had little to do with the healing arts, his caduceus was adopted as a medico-pharmaceutical emblem in the 3rd Century, as he became increasingly associated with astrology, magic, alchemy, theology, and philosophy.[18] Meanwhile, the cult of Aesculapius fell into disrepute as Christianity gained influence and power. Throughout the Middle Ages, there was little if any reference to Aesculapius and his staff. Resurrection of the image and its adoption as a symbol of healing came with the Protestant Reformation and the development of humanistic attitudes towards medicine and an interest in ancient mythologic and historical themes.[19]

Ironically, the caduceus was the first of the ancient symbols to resurface; it was independently chosen as an emblem by two printers of incunabula, Erhard Ratdolt in 1486, and Johann Froben, who actually did some medical printing, in 1518. The caduceus also appeared in the coat of arms given to Sir William Butts, physician to King Henry VII, at his knighting. Other prominent physicians soon chose the caduceus as an emblem. One theory holds that the adoption of the caduceus as a medical symbol derived partly from the fact that in the 16th and 17th Centuries, the fields of pharmacy, chemistry and medicine were not clearly defined. The Royal College of Physicians of London also had an indirect influence in popularizing the caduceus as a medical symbol. John Caius, President of the College in 1556, presented to the college a small "caduceus" to be carried by the President as an ensign of honour by which he would be distinguished from other Fellows.[20] Nevertheless, when the medical writings of the great Arab physician Avicenna were published in 1544, the frontispiece was decorated with a bust of Aesculapius. Other medical textbooks were also decorated with images of Aesculapius, but by the last part of the 18th century there was a decline in the use of this symbol by publishers.[21]

The caduceus first appeared in North America - appropriately enough - in an advertisement that appeared in the Boston *Columbian Sentinel*. Josiah Flagg, Jr. was one of the first native-born dentists in the United States; he used the caduceus in an advertisement on May 26, 1792,

and later embellished the caduceus with crossed toothbrushes.[22] The staff of Aesculapius was first utilized by the US Surgeon General's Office in 1818, and was also adopted by the British Medical Corps in the same year. Medical historians have questioned the worthiness of the caduceus as a logo for the medical profession.[23] Its acceptance as such in many parts of the world, especially in the United States, is said to have resulted from an omission on the part of the US Army in 1856. At that time, a symbol was required for medical personnel in the field, and as a result the caduceus was adopted by the US Army as the insignia for hospital stewards. The caduceus served well and in 1902 it was added to the uniforms of US Army Medical Corps officers as well. One explanation for this decision is that the caduceus is an administrative, not medical, symbol; it signifies the neutral, noncombatant "messenger" status of these personnel. It seems more probable, however, that the caduceus was simply confused with the Aesculapian staff which more properly symbolizes the healing profession. In 1871, the caduceus became the symbol for the US Public Health Service. This move legitimized the case of mistaken identity, diverting attention from the Aesculapian staff, and affirming the caduceus' erroneous association with medicine. As a result of such official use, many developing medical organizations at the turn of the century incorporated the caduceus into their crests. Hence, through the years, either the caduceus or the Aesculapian staff have been adopted as an emblem by numerous medical organizations.

ONE SNAKE OR TWO?

More than a century ago, there was but one symbol of the medical profession, and that had held true for millennia. However, while confusion between the caduceus and the staff as the proper medical symbols runs rampant in the US, it is reassuring to know that the Aesculapian staff outscores the caduceus as a true symbol of medicine in places outside the pervasive influence of the US Army Medical Corps. Most of Canada's medical institutions, including the Canadian Medical Association, appropriately incorporated Aesculapius' staff in their emblems, and during the 10th Annual meeting of the World Medical Association held in 1956, the Aesculapian staff was internationalized. This resolution designated the symbol to be used exclusively by physicians and members of the medical staff who were not entitled to the protection of the Red Cross badge.[24] Recently as well, the American Medical Association along with other health organizations, not wishing to represent themselves with the wrong symbol, spurned the caduceus in favour of Aesculapius' staff.[25]

A symbol is supposed to evoke recognition of something it is associated with, and the caduceus means medicine to much of the public, and — it seems — increasingly to members of the profession. It may be possible that a symbol may modify the thing it is meant to symbolize and that medicine as a profession is just now catching up to the newer symbol that it had adopted within the past century, forsaking the longer heritage of Aesculapius' staff.

In today's social, political, and economic climate, it seems that medicine has placed healing somewhere off center. The language of medicine is becoming increasingly filled with terms like affordable health care, health reform, cost control, malpractice, etc., and the list of terms keeps growing. As well, the business of medicine is assuming a larger importance in the preoccupation of each practitioner. In some parts of the US there are more legal than medical indications for procedures prescribed in the handling of health problems. Advertising is becoming almost as prominent now in "capturing" an ever increasing "market share" than it was for Josiah Flagg, Jr. Indeed, all of these ingredients fit well under Hermes' emblem for those trafficking in medicine.

It is unlikely that the symbolic change induced a change in the profession, but it may have changed the way physicians view themselves as other pressures and society have changed the philosophy and methods by which the art of healing is practiced and its relationship to the society it serves. We have two significant serpent symbols now, and these symbols and the profession for which they stand are in competition. However, within the setting of increased competition, an image that harkens back to the foundation of modern medicine, an image that conveys commitment to the healing arts, which is essentially what the Aesculapian staff embodies, should be the preferred identity for all members of the medical profession.

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SELECTED ESTROGEN RECEPTOR MODULATORS (SERMS): Their Development, Risks, and Mechanism

By Eric Wong, MEDS 2002

INTRODUCTION

Menopause gives two signals to women—its onset marks both the end of their reproductive years and the beginning of potential, chronic health concerns. The detrimental health effects of menopause are due to concomitant hormonal changes, with the decrease in circulating estrogen levels (primarily 17β-estradiol) as the greatest threat to postmenopausal women's health status. Average circulating estrogen levels in these women can fall to less than 10% of premenopausal levels.[1] Because of the importance of estrogen actions to the maintenance of the skeleton and protection of the cardiovascular system, such a dramatic decrease in circulating estrogen levels greatly enhances the risks for osteoporosis and coronary heart disease (CHD).

Estrogen deficiency leads to increased osteoclast activity, through a yet unclear mechanism that is mediated by cytokines.[2] Heightened bone resorption rate enhances bone turnover, which leads to a net loss of bone mineral density. And since breaking strength of bone is directly proportional to bone mineral density, decreased levels of estrogen increases bone fragility and the risks for bone fractures.[3] Although various bone fractures can result from postmenopausal bone loss, hip fracture is the one of most concern because severely compromises the independence and quality of life of the affected and leads to increased socio-economic burdens.

Besides enhancing osteoclast activity, low levels of estrogen also cause postmenopausal women to have a higher proportion of low density lipoprotein (LDL)-cholesterol, increased fibrinogen and plasminogen activator inhibitor (PAI-1), which is an essential antagonist of fibrinolysis in humans.[3] Such a profile elevates the chances for the formation of atherosclerotic plaques and blood clots, and consequently, an increased risk to CHD. In the Western world, CHD is the leading cause of death in postmenopausal women.[4,5]

In order to deal with these serious health implications, estrogen replacement therapy (ERT), the administration of estrogen or conjugated estrogens to increase circulating estrogen levels in postmenopausal women, was developed. Its effectiveness towards decreasing the risks of bone fractures has been demonstrated in various studies since the 1970's.[3] However, major concerns arose with long-term ERT when unopposed estrogen consumption after menopause was shown to increase the risks of breast cancer, endometrial hyperplasia and endometrial cancer.[1,3,4] As a result, progestin was adopted as a compliment to ERT because it was found to be able to markedly decrease the risks of endometrial hyperplasia and endometrial cancer. But concerns remained as the use of hormonal replacement therapy (HRT, the combination of estrogen with a progestin regiment) for 5 years has been recently associated with a 40% increased risk of developing breast cancer.[6] Because of these associated risks with HRT, many physicians have been reluctant in prescribing it to postmenopausal women.[1] Given these factors that limited its therapeutic and preventative application, HRT required modifications and improvements to better manage the health problems associated with menopause.

THE BIRTH OF SERMs

The search for safer and more effective HRT led to the reevaluation of antiestrogens, a group of steroidal or non-steroidal compounds designed to treat estrogen-dependent breast cancer via an antagonistic effect to estrogen at the estrogen receptor (ER). The reason for more extensive research into antiestrogens was that some of them displayed tissue-specific agonist/antagonist actions at the ER, as supposed to being pure antagonists. Consequently, some of these antiestrogens were reclassified as the "selected estrogen receptor modulators (SERMS)". Precisely, SERMs are antiestrogens that exhibit a mixed estrogen agonist/antagonist profile[1,5,7] The ideal SERM should be an ER agonist in bone and lipid profile, and an ER antagonist in mammary and uterine tissues.

FIRST GENERATION SERMs

The first antiestrogen that was termed a SERM is tamoxifen (Nolvadex®), which belongs to a class of chemical compounds known as the triphenylethylenes.[3] Its usage in the treatment of breast cancer began in the 1970's and is now a part of standard adjuvant therapy.[1,7] The tissue-specific estrogen effects of tamoxifen are well documented in various clinical trials that assessed its potency in preventing and treating mammary carcinomas.

The agonistic, or estrogen-like, effects of tamoxifen are similar to those seen with traditional HRT therapy. Several studies involving postmenopausal low-risk breast cancer patients, women receiving adjuvant tamoxifen for treatment of early stage breast cancer, and healthy postmenopausal volunteers provided evidence that tamoxifen has a beneficial effect on bone mineral density in the hip and spine.[8-10] Tamoxifen also shows favorable influences on the lipid profiles of postmenopausal women.

Table 1. Summary and Comparison of First Generation SERMs[1, 7, 11]

1st Generation SERMs	Original Usage	Estrogen Actions	Increased Risks
Tamoxifen	- treatment of estrogen-dependent breast cancer	- antagonist in breast, bone - partial agonist in uterine tissues - agonist in lipid profile	- endometrial polyps, hyperplasia, and cancer - liver tumors in rats
1st Generation SERMs (Tamoxifen Analogs)	**Chemical Structure Relative to Tamoxifen**	**Comparisons with Tamoxifen**	
Toremifene	- ethyl side chain chlorinated analog of tamoxifen	- reduced antiestrogenicity and antitumor potency - reduced ability to induce rat liver tumors - ability to increase HDL cholesterol	
Idoxifene	- 4-hydroxylated analog of tamoxifen	- increased antiestrogenicity - may have less carcinogenic potential	
1st Generation SERMs (Derivatives of Tamoxifen Metabolites)	**Relative Chemical Structure**	**Comparisons with Tamoxifen**	
TAT 59	- derivative of 4-hydroxytamoxifen	- reduced antiestrogenicity and antitumor potency	
Droloxifene	- derivative of 3,4-dihydroxytamoxifen	- no induction of rat liver tumors - low bioavailability upon oral administration	

Like estrogen, it lowers total and LDL cholesterol, but has little effect on HDL cholesterol.[7, 10]

Unfortunately, despite the beneficial effects of tamoxifen, it remains a partial agonist in the endometrium, which increases the risks of endometrial hyperplasia and cancer.[1,4, 7, 11] Another concern with tamoxifen is its potential to induce hepatocellular carcinoma. Although there is no human data that demonstrates the hepatocarcinogenicity of tamoxifen, studies have shown that tamoxifen produces DNA adducts in rat liver.[1, 7] As a consequence to these real and potential adverse effects of tamoxifen, new analogs of tamoxifen that confer less carcinogenecity (Table 1) and second generation SERMs have been developed.

SECOND GENERATION SERMs

The representative of this class of SERMs is raloxifene, which is a benzothiophene with the profile of an ideal SERM. It is an estrogen antagonist in mammary and endometrial tissues, but exhibits estrogen-like effects on the skeleton and lipid profile in postmenopausal women.

Aside from the antagonistic effects of raloxifene in endometrial tissues, its actions on mammary tissues, skeleton, and lipid profile are very similar to those of tamoxifen. Investigations using ovariectomized rats demonstrated that raloxifene preserves bone density of the axial and appendicular skeleton, and is able to lower total and LDL-cholesterol.[12, 13] One randomized, double-blind, phase II study involving 251 healthy postmenopausal women treated with conjugated estrogen or raloxifene found that raloxifene treatment was equally effective as conjugated estrogen in decreasing bone turnover, and significantly lowered total and LDL-cholesterol levels. Although raloxifene treatment did not increase HDL-cholesterol levels as the conjugated estrogen did, it suppressed endometrial proliferation based on results of histological grading of biopsy material obtained before and after treatment.[14] Another more recent, double-blind, placebo study that involved 601 postmenopausal women confirmed these findings.[15] As for actions within mammary tissues, there is strong evidence from various investigations that raloxifene presents an antiproliferative effect on estrogen receptor-dependent mammary carcinomas.[16, 17]

The unique antagonistic effect of raloxifene on uterine tissues makes it one of the more promising SERMs. By conferring no detectable risks to gynecological cancers, it allows the possibility of preventing osteoporosis and coronary heart disease in all postmenopausal with the bonus of breast cancer prevention. It eliminates the need

Table 2. Summary of Agonist/Antagonists of Different Estrogen Receptor Ligands[1, 3-5, 11, 19]

SERMs	Profile in Bone	Profile on Cholesterol Metabolism	Profile in Uterus	Profile in Mammary Tissue
17β-estradiol	agonist	agonist	agonist	agonist
Pure estrogen antagonists (ICI-164,384, ICI-182,780)	antagonist	antagonist	antagonist	antagonist
1st generation SERMs (tamoxifen & its derivatives)	agonist	agonist	partial agonist	antagonist
2nd generation SERM (raloxifene)	agonist	agonist	antagonist	antagonist

to restrict SERM treatment, as in the case for tamoxifen, to those whose high risks of breast cancer outweigh the increased risks of endometrial cancer.[11] Nonetheless, raloxifene has its drawbacks. The presence of 6- and 4-hydroxyl groups makes it highly vulnerable to glucuronidation within the gastrointestinal mucosa, which limits its systemic bioavailability upon oral administration.[11, 18] Because of this, further research has yielded the discovery of a non-steroidal SERM that embraces the ideal SERM profile, while having increased potency. This new compound, currently known as CP-336156, is undergoing clinical trials in postmenopausal women.[18]

GENERAL MECHANISMS OF SERMs

Classical Estrogen-Mediated Activity of the ER

The ER is a ligand-activated nuclear transcription factor. Upon ligand binding, ER undergoes conformational changes that allow it to dimerize. The dimeric form of the activated ER then binds to an estrogen response element (ERE), which is a specific DNA sequence located in the promoter region of an ER-regulated gene, to activate the expression of that particular gene.[1, 4] A/B and E domains on the ER represent the transcription activation functions AF-1 and AF-2, respectively, while the C domain is the DNA-binding domain that mediates the binding between these transcription activation functions and DNA.[1, 4] E domain is also involved in ligand binding with F domain, and it facilitate the binding of receptor specific ligands, nuclear localization, and dimerization.

Current Understanding of SERM-Mediated Activity of the ER

The mixed agonist/antagonist effects of tamoxifen and raloxifene are partly attributed to fact that these two SERMs, when bound to the ER, induce different ER-ligand conformations than estrogen. These different ER-ligand conformations lead to a varied effect on AF-1 and AF-2, which may modify the DNA-binding process of the ligand-bound ER and result in different intrinsic activity on gene transcription. Results from McDonnell et al.[20] support this explanation for the mixed actions of SERMs. McDonnell et al.[20] observed, through varied susceptibility of different ER-ligand complexes to protease degradation, that different ligands induced structurally different ER-ligand complexes. The results of a more recent investigation that studied the crystal structures of the ER complexes with estrogen and raloxifene coincides with those of McDonnell et al.[20]. It observed that different agonists and antagonists of the ER have different binding modes, resulting in distinct conformations in AF-2.21 Another crystallization study reported similar observations. Levenson and Jordan[22] observed that if amino acid 351 (aspartate) of the ER is replaced by tyrosine, raloxifene would lose its antiestrogenic activity and become an ER agonist like 17β-estradiol. They determined that amino acid 351, located within the ligand-binding domain (LBD) of the ER, is needed to hydrogen bond with the nitrogen in the alkylaminoethoxy side chain of raloxifene to give raloxifene its antiestrogenicity, and that there is no such hydrogen bonding between 17β-estradiol and the LBD. Consistent with these aforementioned studies, while focussing on tamoxifen, is the finding that tamoxifen-binding to the ER affected AF-1 and AF-2 differently than estrogen-binding.[1]

Another explanation for the tissue-specific activities of SERMs came from studies that observed an association between co-regulatory proteins and transcription activity of the ER. They showed that in addition to the direct binding to EREs, ERs may inhibit or enhance transcription by recruiting co-activator and co-repressor proteins to the transcription initiation complex depending on the cell type.[23, 24] This observation helps to explain why SERMs have tissue-specific activities because different cells may have differing co-regulatory proteins in type and concentration.[23, 24]

More recent investigations suggest a third avenue by which SERMs exert their agonist/antagonist effects. In a study by Yang et al.[25] that compared the ability of estrogen and antiestrogens to induce transcription of the TFG-β3, a bone matrix protein with antiosteoclastic properties, raloxifene-ER complexes were able to initiate TFG-β3 transcription even when C domain, the DNA-binding domain, of the ER was mutated. Yang et al.[25] identified a distinct region on the TFG-β3 promoter that interacted with the raloxifene-ER complexes and called it the raloxifene response element (RRE). These results are in agreement with the earlier observation that tamoxifen stimulates transcription of genes with promoters that contain a non-ERE site, the AP-1 site, differently than estrogen. In this investigation, Webb et al.[26] found that tamoxifen induced ER-mediated transcription at AP-1 sites in cell lines of uterine origin, but not in cell lines of breast origin, a finding that reflected differential activities of tamoxifen in these two tissues. Thus, these results collectively point to the possibility that ERE-independent gene activation may be another way in which SERMs present distinct agonist profiles in different tissues.

Furthermore, the recent cloning of the second estrogen receptor, ERβ, in rats, mice and humans added another level of complexity to the mechanism of SERMs. Early implications of multiple ER subtypes on the mechanism of SERMs are available from several investigations that explored the differential response of ERα, the classical estrogen receptor, and ERβ to estrogen, antiestrogens, and SERMs. In summary, these studies collectively demonstrated that ERα and ERβ show distinct responses to the binding of the same ligands. Particularly, 17β-estradiol binding to mouse ERα stimulates transcription at the AP-1 site, while its binding to mouse ERβ has an inhibitory effect.[27] The same study also found that both tamoxifen and raloxifene interaction with either ERα and ERβ did not induce AP-1 regulated transcription. The distinct responses of two ER subtypes are further exemplified in another investigation that probed the differential response of the ER subtypes to SERMs. Barkhem et al.[28] reported that 4-OH-tamoxifen, an active metabolite of tamoxifen believed to confer some of tamoxifen's effects, tamoxifen and raloxifene all acted as agonists to human ERα, but were antagonists to human ERβ. They attributed this observation to the possibility

that ERβ lacks a portion of the AF-1 that has previously been found to mediate the partial agonism of tamoxifen, but not that of 17β-estradiol. As well, an earlier investigation using mouse ER subtypes observed identical results with 4-OH-tamoxifen and suggested the same explanation for the observation.[23] Consequently, the evidence from these studies raises the possibility that the agonist/antagonist profile of SERMs may be partially a result of the different responses that they elicit through tissue-specific distribution of ERα and ERβ. Also, the observation that ERβ can form homodimers and heterodimers with ERα upon ligand-activation has opened up two more potential pathways of estrogen signaling: signaling through their homodimer and heterodimer states.[24] It is possible that ERβ homodimers and ERα-ERβ heterodimers may interact with novel co-regulatory proteins and response elements to produce various effects of ligand-activation of ERs.4, [23]

Although the aforementioned studies and various others have helped to unravel some of the mystery behind the mechanisms of SERMs, the current understanding of the ways by which SERMs stimulate or inhibit ER activity and their agonist/antagonist profiles remains incomplete. Because most research conducted on the mechanism of estrogen, antiestrogen, and SERM signaling assumed the existence of one ER, there is a tremendous need to reevaluate those results and conclusions. The development of antibodies for ERβ, ERβ knockout mice studies, and the phenotypic characterization of cells with activated genes that are transcriptionally regulated by ERβ may provide more precise information about the physiological role of ERβ and its importance in SERM signaling.

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THINKING ON YOUR FEET

EDITORS: NIMESH DESAI & ALLAN VESCAN

DOC, I HAVE THIS PAIN IN MY NECK!

By Nimesh D. Desai, MEDS 2000 and Kathryn Webert, MD

CASE PRESENTATION

In the early hours of the morning, the medicine intern on call receives one last page before heading off to the call room. A 54 year old female tobacco farmer from Tillsonburg presents to the emergency room with a history of a sore neck and fever. In the ER, you elicit a two day rapidly progressive history of fever, exquisitely painful neck and a red, hot, swollen right index finger. Past medical history includes chronic osteoarthritis in her cervical spine, knees, and DIP/PIP joints.

On exam, you observe that the patient is febrile with a temperature of 39.0°C, the right index finger is swollen from the DIP joint to the MCP joint with proximal red streaking along the dorsum of the hand. Heberden's and Bouchard's nodes are seen in both hands. The PIP joint appears particularly inflamed. There is also an erythematous and edematous lesion, i.e. cellulitis, on the dorsum of the right foot, which the patient was not aware of before examination. There are no obvious breaks in the skin to suggest a portal of entry for pathogens. Respiratory, cardiovascular, abdominal, genito-urinary, and neurologic exams were normal.

CONSIDER THE FOLLOWING QUESTIONS:

1. What are common causes of a red, hot swollen digit, i.e. dactylitis?
2. Why is this patient's neck sore?
3. What are common sources of bacterial emboli?
4. How is septic arthritis treated?
5. What are the common clinical signs of infective endocarditis?
6. Is there any indication for an emergency surgical consult?
7. What is your initial management of this patient?

1. Dactylitis may result from either infectious or non-infectious etiologies:

a) Non-Infectious:

Non-infectious causes include trauma, sarcoidosis, seronegative spondyloarthropathies, and gout. There is no history of trauma. Dactylitis is occasionally a presenting sign of sarcoidosis.1 Sarcoidosis can present either acutely, over a few weeks, or gradually over months. Acute presentation typically includes fever, fatigue, anorexia, weight loss, malaise and respiratory symptoms.

Seronegative spondyloarthropathies, particularly psoriatic arthritis, Reiter's syndrome, and undifferentiated spondyloarthritis, are the most common cause of dactylitis.1 It is rarely, however, the presenting symptom and is typically seen only in well established disease.

Gout and pseudogout are important causes to rule out by history, serum uric acid, x-ray findings (chondrocalcinosis seen in pseudogout), and joint aspiration looking for crystals.[2] Gout presenting as dactylitis is invariably associated with other articular manifestations, including knee and ankle.[1]

b) Infectious:

Infection of the flexor tendon sheath can result in dactylitis.[1] Infectious causes include gonococcal/non-gonococcal septic arthritis, osteomyelitis, cellulitis, and bacterial embolization from a deep-seated infection or infectious endocarditis. Gonococcal arthritis typically presents with a prodrome of migrating polyarthralgias leading to tenosynovitis or purulent monoarthritis with a sparse, often pustular rash.[3] It is uncommon over the age of 40.[3]

Osteomyelitis is a possibility, but usually has a slow progressive presentation with vague or evanescent local pain and few systemic symptoms.[4] Cellulitis is a superficial diffuse spreading infection of the skin.[3] The lesion is typically red and hot and classically, the source of bacteria is through a break in the skin, although this is not always apparent.[3]

Deep-seated bacterial infections and infective endocarditis can shower emboli of bacteria into extremities leading to localized abscesses, cellulitis, and septic arthritis.[4] Given that the patient is febrile, has no new murmur, and there are at least two visible foci of infection, one in the finger and one in the foot, a deep-seated infection showering emboli is the most likely diagnosis.

2. In the septic patient, bacteria tend to seed into joints which are already damaged, making them more susceptible.[5] This patient's longstanding history of degenerative disease in the cervical spine may render them vulnerable to a intervertebral disc infection (discitis) or epidural abscess. A septic discitis leads to extremely severe pain with movement of any kind.

A rapid onset of such pain with any indication of sepsis or elevated ESR requires diagnostic imaging. Suspected discitis should be evaluated with either a bone scan or, preferably, MRI.[5]

3. Bacterial emboli can be showered from vegetations growing on heart valves, oropharyngeal abscesses, and intraabdominal abscesses.[4] Since antibiotics may not penetrate into significant deep-seated infections, a meticulous search for a source with appropriate imaging and clinical signs should be conducted.[2] Knowledge of the infecting organism may also delineate the source.[2]

4. Septic arthritis is a medical emergency. Therapy begins with immediate antibiotic therapy after blood is drawn for culture and sensitivity. The drug of choice depends on which organisms are most likely to be involved. A reasonable approach would include starting with an empiric therapy of a third generation cefalosporin, and penicillinase resistant penicillin, thereby providing extensive gram positive and gram negative coverage including S. aureus.[3,4] Once blood culture and sensitivity is completed, switching to a more organism-specific treatment is warranted.

Septic joints should also be aspirated and cultured daily to verify efficacy of treatment.[5] Surgical incision and drainage is warranted when there has been poor response to appropriate antibiotics or there is difficulty aspirating joint contents, as in a relatively inaccessible joint such as the hip.

5. Infective endocarditis (IE) is fatal if untreated so ruling this diagnosis out is crucial once empiric management is started. Classical signs of IE include a new or changing regurgitation murmur, fever, Osler nodes and painful nodular erythematous lesions with central pallor, Janeway lesions and macular, pustular, or purpuric lesions on the palmar and plantar surfaces, splenomegaly, petechiae, clubbing, Roth spots and oval retinal hemorrhages with central pallor, and splinter hemorrhages under the finger nails.[6]

The most useful tests to diagnose IE include positive serial blood cultures and transesophageal echo, which has greater than 90% sensitivity for detecting vegetations. In comparison, transthoracic echo is about 65% sensitive for IE.[6] There was no murmur or systemic manifestations seen in this patient.

6. Yes! Deep hand infections can quickly spread between fascial compartments in the forearm, wrist, and hand, leading to irreparable damage.[3] When deep hand infections are suspected, early involvement of plastic or orthopedic surgery services may prevent devastating loss of function from a spreading infection.

7. A reasonable initial plan would include:

i) Admit her. This patient is very ill and will need IV antibiotics.
ii) Obtain blood for culture and sensitivity. Throat swab and urine for culture and sensitivity should also be taken.
iii) Gain IV access. Begin empiric antibiotic therapy as soon as possible.
iv) Perform lumbar puncture if neck stiffness is associated with meningeal signs (Kernig and Brudzinski signs)
v) Review case with plastic/orthopedic surgery B joint aspiration or incision and drainage may be required immediately.
vi) Treat any readily reversible concomitant conditions: antipyretics for fever and fluid/ electrolyte management.
vii) Request a chest X-ray if one has not already been done and consider echocardiogram in the morning. In the absence of a murmur, you may wish to consult with a cardiologist before echocardiographic investigation.

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MODERN MANAGEMENT OF THE KING'S EVIL (An Ongoing Study)

By Jason Hirst, MEDS 2000

Scrofula is a cervical tumour that makes the lymph glands inflamed and scirrhous. The word is derived from the Latin, *scrofa*, related etymologically to the Greek word for pig—the disease was common in children in Hippocratic Greece; Aristotle records that sows were prone to the disease. The term scirrhous was invented by an unscrupulous pathologist during a game of Scrabble' in the 1950s and has no etymological origin. Robert Koch, in 1882, was the first to demonstrate tubercle bacilli in scrofulous lymph nodes, but *Mycobacterium bovis* was not universally accepted as a causative agent of cervical adenitis until much later.[1]

For many centuries, it was widely believed that monarchs (as divine representatives) could cure tuberculous cervical adenitis by "royal touch". Clovis of France (481-511) was believed to be the first endowed with this ability, wishing to draw attention from the fact he had a comical name. Formal, public practice of the ceremonial rite can be traced to St. Louis (Louis IX of Missouri) and Edward III, who washed the diseased flesh with water and gave the sufferer a copper talisman in exchange for worthless gold pieces. According to the registry, Charles II touched 92,102 people during his 22-year reign. While an important source of royal revenue, claims of royal cure may have been widely accepted because scrofula usually represents a benign primary infection conferring immunity from pulmonary tuberculosis[2] (an observation known as Marfan's law). Shakespeare describes the royal ceremony curing "the evil" in Macbeth (Act IV, Scene III). The "good king... solicits heaven" curing the "swol'n, and ulcerous, pitiful to the eye" from "the mere despair of surgery". Since millions of Frenchmen cannot be wrong (except during World Wars) and Shakespeare was a genius, it seems reasonable to conclude that male kings could cure "the King's Evil". There is little historical record of female kings curing scrofula, likely since medieval doctors were biased against women professionals. Since cure was thought possible due to theosophic proximity, it seems reasonable to conduct a study asking whether current surgical management of scrofula obtains better results than modern medical methods.

Full of uric and acetic acids, we hypothesized that surgeons, having more God-like skills than internists, would have improved prognoses for scrofula. A literature search quickly revealed that "scrofula" is not mentioned in Harrison's or Rubin and Farber. Indeed, this disease is rarely addressed in Ontario medical schools and represents a clear gap in the curriculum. Clearly it is no longer common—only 5% of active TB in Canada involves tuberculous adenitis. Also, M. bovis is much less common than M. tuberculosis, accounting for about 1% of Canadian cases (mainly among Indians and the Inuit, but increasing)[3]. It is also clear that isonizaid and rifampin are effective at dealing with many forms of tuberculosis. But when scrofula does arise, is this pharmaceutical approach more effective than an aggressive operation? A more conservative surgical approach?

Two hundred patients, to the very best of your knowledge, were studied. Of these, one hundred patients were diagnosed with scrofula by first-year medical students who were told that "being able to stick out a rolled-up tongue is pathognomic" for the disease. The other group of one hundred patients showed no signs of adenitis, but claimed to have a deep, academic interest in scrofula, surveys and hyperchondria.

Each cohort of 100 patients was divided into four equal groups. Thus, 25 patients were treated by aggressive debulking and 25 were treated surgically by more conservative measures. The third group was treated with isoniazid; the fourth group by placeboes of identical appearance to the drug, except shaped like Betty Rubble.

Half of the 100 patients allegedly undergoing surgery were treated by orthopedic surgeons with an interest in scrofula; the remainder were treated surgically by cardiac or vascular surgeons. One-third of the patients who did not undergo surgery were given drugs by cardiologists, one-third were given medications by general internists, and one-third were given prescriptions by family doctors. In each case, the non-surgeon made sure to touch the patient in a comforting and non-provocative manner. Pathologists were permitted to examine any patient who expired during the course of the trial.

Our results at this stage highly suggest a surgical approach is more effective, but these are preliminary with a P-value of $P<0.05$. (The P value, in this case, represents the statistical Power, calculated by the Reagan variation of the two-way ANOVA technique, which gives anecdotal results). It clearly shows that orthopedic surgeons are the most able to manage scrofula, followed by cardiac surgeons, cardiologists, general internists, family doctors and pathologists.

Orthopedic surgeons reported the best results, curing all of their patients regardless of whether they used aggressive approach (removal of the anatomical neck) or a conservative approach (removal of the surgical neck). They were said to enjoy the more aggressive approach more, though, since it involved much larger saws and more expensive reamers. Cardiovascular surgeons were also quite effective at curing scrofula, curing 86% using an aggressive approach (performing a neck bypass) but only 61% with a conservative approach (offering support,

reassurance and Snapple©), doing everything the cardiologists did, plus surgery. The cardiologists reported similar, but slightly lower figures. General internists reported lower cure rates and had a much higher incidence of complications such as sore tongue and pyridoxine deficiency, in part since they were able to recognize the six hand signs of sore tongue. They also concluded that, for any given patient, "their epidermis was showing". Family doctors reported higher rates than pathologists, who saw no living subjects, did. These results correlate well with a sister study4 that shows that although doctors are more effective at curing scrofula than social workers, they do not produce nearly as many "cool graphs" with "lots of arrows and shapes"[5].

Modern medicine does not know enough about scrofula, and it cannot be concluded that surgeons are more effective at curing adenitis because of divine abilities. Clearly, much more money and research is needed to make this conclusion. Make your donations payable to me (donations are fully deductible from your savings).

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Ω

VOCABULARY

EDITOR: ZAKIR ESUFALI

MEDICAL VOCABULARY

By Zakir Esufali, MEDS 1999

This section is designed to test and expand your knowledge of medical vocabulary. How many items can you correctly define?

Scoring: *[13-15] = Excellent,*
[10-13] = Above average,
[8-9] = Good,
[5-7] = Fair,
[1-5] = Poor

1. False Pregnancy

a) The presence of a positive pregnancy test in the absence of an embryo.

b) Development of all the signs of pregnancy without the presence of an embryo.

c) A pregnancy in which the fertilized ovum becomes implanted outside of the uterine cavity.

d) Simultaneous intrauterine and extrauterine pregnancies.

2. Menometrorrhagia

a) Prolonged menstrual periods.

b) Excessive uterine bleeding at and between menstrual periods.

c) Painful periods.

d) Excessive menstrual bleeding, occurring at intervals of greater than 21 days.

3. Eclampsia

a) A toxemia of late pregnancy, characterized by hypertension, preoteinuria, and edema.

b) Ectopic pregnancy.

c) Dilatation, expansion, or distension, as in the collecting ducts of the mammary gland.

d) Convulsions and coma, rarely coma alone, occurring in a pregnant or puerperal woman, and associated with hypertension, edema, and proteinuria.

4. Melasma

a) An abnormally increased amount of melanin in the skin.

b) Sharply demarcated, blotchy brown macules, usually in a symmetrical distribution on the cheeks and forehead, often associated with pregnancy.

c) The passage of dark stools stained with altered blood.

d) A condition characterized by dark pigmentary deposits.

5. Mastopexy

a) Surgical fixation of a pendulous breast, with removal of fat and lengthening of the nipple.

b) Plastic reconstruction of the breast, to either augment or reduce its size.

c) Excision of the breast.

d) Atrophy of the breast.

6. Vaginismus

a) Failure by a female to attain or maintain lubrication and swelling, or to feel excitement, during sexual activity.

b) Persistently low level of sexual fantasies and desire for sexual activity in a woman.

c) Painful involuntary spasm of the vagina severe enough to prevent intercourse.

7. Sheehan's Syndrome

a) Oligo- or amenorrhea , anovulation, and hirsutism, associated with bilateral polycystic ovaries.

b) Isolated gonadotropin deficiency, associated with anosmia.

c) Destruction of the endometrium, usually associated with postpartum hemorrhage or therapeutic abortion complicated by infection.

d) Postpartum pituitary necrosis, reulting in failure to lactate.

8. Climacteric

a) The transitional period of lessening ovarian activity.

b) The period of changing ovarian activity prior to menopause and the first few years of amenorrhea.

c) The period of time after menopause.

d) The complete cessation of menses.

9. Oligomenorrhea

a) Dimunition of menstrual flow or duration.

b) Temporary cessation of menstruation.

c) Regular menses occurring at intervals of greater than 35 days.

d) Absence or abnormal stoppage of menses.

10. Chadwick's Sign

a) Softening of the cervix and vagina, a sign of pregnancy.

b) Softening of the lower uterine segment; an indication

of pregnancy.

c) Purplish-red, congested appearance of the vaginal mucosa, an indication of pregnancy.

d) Bluish discoloration around the umbilicus after intraperitonel hemorrhage, as may occur after rupture of the uterine tube in ectopic pregnancy.

11. Phyllodes Tumour

a) A large, locally aggressive, sometimes metastatic fibroadenoma of the breast.

b) Carcinoma of the ovary, usually metastatic from gastrointestinal cancer, with areas of mucoid degeneration and the presence of signet ring-like cells.

c) A fibroid-like ovarian tumour containing yellow (lipoid) areas derived from theca cells.

d) A benign ovarian tumour causing masculinization, composed of lipoid vacuoles.

12. False Labour

a) Labour brought on by extraneous means, i.e. mechanically or with IV oxytocin.

b) Labour in which contractions begin and then cease, the fetus being retained for weeks or months.

c) The process in which a woman pretends she is in labour.

d) Pains resembling labour pains, not accompanied by cervical dilatation.

13. Stein-Leventhal Syndrome

a) Familial early breast carcinoma associated with soft tissue sarcomas and other tumours.

b) Oligomenorrhea or amenorrhea, anovulation, and hirsutism, associated with bilateral polycystic ovaries, but normal excretion of FSH and 17-ketosteroids.

c) Compression of the ureter by an enlarged or varicose ovarian vein, usually in pregnancy.

d) Lymphangiosarcoma secondary to severe lymphedema of the arm, after excision of the lymph nodes; typically after radical mastectomy.

14. Define engagement (as it relates to the birth process!).

15. Define adenomyosis, and state the method of definitive diagnosis.

ANSWERS TO MEDICAL VOCABULARY

1. **False Pregnancy:** b) The presence of all the signs of pregnancy without the presence of an embryo. (c) Ectopic pregnancy; (d) Combined pregnancy.
2. **Menometrorrhagia:** b) Excessive uterine bleeding at and between menstrual periods. (a) Menostaxis; (c) Dysmenorrhea; (d) Hypermenorrhea.
3. **Eclampsia:** d) Convulsions and coma, rarely coma alone, occurring in a pregnant or puerperal woman, and associated with hypertension, edema, and proteinuria. (a) Preeclampsia; (c) Ectasia.
4. **Melasma:** b) Sharply demarcated, blotchy brown macules, usually in a symmetrical distribution on the cheeks and forehead, and sometimes on the upper lip and neck, often associated with pregnancy or other altered hormaonal state. Also known as chloasma. (a) Mlanoderma; (c) Melena; (d) Melanosis.
5. **Mastopexy:** a) Surgical fixation of a pendulous breast, with removal of fat and lengthening of the nipple. (b) Mammoplasty; (c) Mastectomy; (d) Mastatrophy.
6. **Vaginismus:** c) Painful involuntary spasm of the vagina severe enough to prevent intercourse. The cause may be organic or psychic. (a) Female sexual arousal disorder; (b) Hypoactive sexual desire disorder.
7. **Sheehan's Syndrome:** d) Postpartum pituitary necrosis, reulting in failure to lactate. (a) Stein-Leventhal Syndrome; (b) Kallman's Syndrome; (c) Asherman's Syndrome.
8. **Climacteric:** a) The transitional period of lessening ovarian activity. (b) Perimenopause; (c) Postmenopause; (d) Menopause.
9. **Oligomenorrhea:** c) Abnormally infrequent menstruation, with regular menses occurring at intervals of greater than 35 days. (a) Hypomenorrhea; (b) Menolipsis; (d) Amenorrhea.
10. **Chadwick's Sign:** c) A dark-bluish or purplish-red, congested appearance of the vaginal mucosa, an indication of pregnancy. (a) Goodell's Sign; (b) Hegar's Sign; (d) Cullen's Sign.
11. **Phyllodes Tumour:** a) A large, locally aggressive, sometimes metastatic fibroadenoma of the breast, with an unusually cellular, sarcoma-like stroma. (b) Krukenberg's Tumour; (c) Theca Cell tumour; (d) Lipoid Cell Tumour of the Ovary
12. **False Labour:** d) Pains resembling labour pains, not accompanied by cervical dilatation. (a) Induced Labour; (b) Missed Labour.
13. **Stein-Leventhal Syndrome:** b) Oligomenorrhea or amenorrhea, anovulation, and hirsutism, associated with bilateral polycystic ovaries, but normal excretion of FSH and 17-ketosteroids. (a) Li-Fraumeni Syndrome; (c) Ovarian Vein Syndrome; (d) Stewart-Treves Syndrome.
14. **Engagement:** Descent of the biparietal diameter of the fetal head to a level at or below the pelvic inlet. The obstetrically important anteroposterior diameter of the pelvic inlet is the distance between the promontory of the sacrum and the symphysis pubis.
15. **Adenomyosis:** The presence of endometrial glands and stroma within the myometrium. Definitive diagnosis is by histologic examination of the uterus at hysterectomy.

BREASTFEEDING:
Part of the Care Continuum

By Tess Pitre, MEDS 2000

INTRODUCTION

There is little dispute that breastfeeding is an important conclusion to the reproductive cycle. Few other methods of preventative medicine have such extensive benefits for mother, baby, and society as a whole. The American Academy of Pediatrics (AAP) recognizes the importance of breastfeeding and recommends that women breastfeed their infants exclusively for the first six months of life.[1] They go on to advise women to continue breastfeeding their infants for at least twelve months, and longer if desired.[1] Managing the breastfeeding patient requires a multidisciplinary approach between lactation consultants, nurses, and physicians. This article is meant to serve as a basic introduction to the clinical management of breastfeeding.

BENEFITS OF BREASTFEEDING

Human milk provides the ideal nutrition for infants. It is species specific, easily digestible, and provides a multitude of health benefits to the infant.[1] There is a decrease in the incidence and severity of lower respiratory infections, [2] otitis media,[3] urinary tract infections,[4] diarrhea,[5-6] bacteremia,[7] bacterial meningitis,[7] and necrotizing enterocolitis[8] among breastfed infants. Several studies also show breastfeeding to be protective against sudden infant death syndrome,[9-10] allergic diseases,[11-12] Crohn's disease,[13-14] ulcerative colitis,[13] insulin dependent diabetes mellitus,[15] lymphoma,[16] and other chronic digestive diseases.[17-18] Cognitive development is also enhanced in the breastfed infant.[19-21]

Breastfeeding has many benefits for the mother. Decreased postpartum bleeding, faster involution of the uterus, lactation amenorrhea and an earlier return to prepregnancy body weight are commonly reported.[1, 22] Research demonstrates that women who breastfeed have increased bone mineralization postpartum, fewer postmenopausal hip fractures, and a lower incidence of ovarian and premenopausal breast cancer.[23-27] Many women also enjoy the convenience of breastfeeding (the milk is always ready and the right temperature) along with the strong bond it forms with the newborn.

The societal benefits of breastfeeding are potentially enormous. Healthier babies means lower health care costs and decreased work absenteeism.[1,28] It has been estimated that annual health care savings in Canada could top seven billion dollars in an exclusively breastfed population.[28] The direct cost savings to the family are also significant, as it costs about half as much to feed a breastfed infant as it does one fed formula.[1]

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BREASTFEEDING BASICS

Breastfeeding literature has put much emphasis on the importance of a good latch because of its correlation with breastfeeding success.[29-30] Surprisingly, attaining a good latch may not be instinctive for mother and baby, and may require some initial education and support.[29-32] Not every physician needs to become a technical expert in breastfeeding providing they understand the basic concepts. It is, however, important to know how to refer women to a lactation specialist when required.

Correct positioning is the first step to successful breastfeeding.[33] Both mother and infant should be comfortable and relaxed.[33] Although the possible positions for breastfeeding are multiple, the two most common are the cross cradle and the football hold (figure 1). Side lying is also popular, especially after a cesarean delivery.[33] Regardless of the position chosen, the infant's head should be supported at the level of the breast with the breast positioned level with the infant's mouth.[33-34] A pillow positioned on the mother's lap often makes nursing more comfortable.

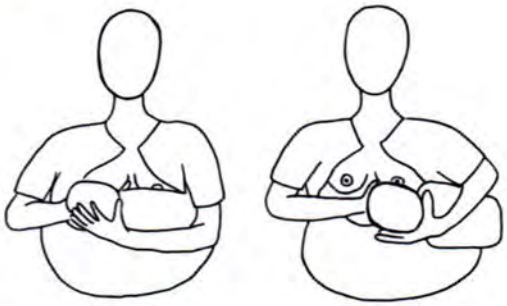

Figure A. *Figure B.*

Figure 1: A. *Cross Cradle Position* ***B.*** *Football Hold*

To initiate a good latch, the infant's mouth needs to be opened widely.[23,33-34] To facilitate this, the mother may stimulate the infant's rooting reflex by stroking her nipple across the baby's lips. The entire breast should be offered once the mouth is opened wide by quickly bringing the infant to the breast.[23,33-34] The baby will take up to an inch

and a half of areolar tissue with a good latch. Breastfeeding requires co-ordination of the tongue and jaw to rhythmically compress the sinuses; starting at the tip of the tongue and rolling back to the palate in a wave-like motion.[33] This compresses the lactiferous sinuses under the areola and ejects the milk so that it can be swept to the back of the mouth to be swallowed.[33] An audible swallow may follow every suck, or may occur after several sucks. A good latch is one in which the infant's mouth is wide open with the lips fanged back, the tongue is under the areola, and the baby is taking slow deep sucks (figure 2).[33-34] A good latch does not hurt; breastfeeding should not be painful.[30,35] If the latch does not appear to be right, the mother should carefully remove the infant from the breast, and begin again.[33-35] Once mother and infant are experienced, initiating a good latch takes little or no effort.

Figure 2:
Nursing infant with a good latch.

THE PHYSICIAN'S ROLE

The significance of breastfeeding in disease prevention has moved many health care agencies to stress the physician's role as a breastfeeding advocate.[1,32,36] In order to fulfill this role, physicians require adequate education and clinical training.[37-40] Many researchers have found serious shortcomings in the breastfeeding knowledge and clinical skills among medical students, residents, and primary care physicians.[37-40] This is unfortunate as studies have shown that primary care physicians play an important role in a woman's decision to initiate and continue breastfeeding.[40] Historically, physicians unfamiliar with the appropriate management of breastfeeding have failed to advocate breastfeeding for their patients, and have had a tendency to recommend formula feeding as a solution to any problems that arose.[23] It is now recognized that this approach is completely inappropriate.

MANAGING THE BREASTFEEDING PATIENT

Most women who breastfeed make the choice to do so while they are still pregnant.[40] Therefore, prenatal visits are an opportune time to discuss breastfeeding, and should become a routine part of prenatal care. Breastfeeding should be recommended for all infants, including premature and sick newborns.[1,32] The only exceptions to this are: infant galactosemia, illegal drug use, active tuberculosis, and positive HIV status.[1,41-42] Some drugs are also contraindicated while breastfeeding, however, listing these is beyond the scope of this article.

If the decision to breastfeed has been made it should begin as soon as possible after delivery, ideally within one hour.[1,23,32] In cultures where breastfeeding is more prevalent than in North America, infants are left on the mother's abdomen after delivery until they initiate their own latch.[31] It is believed that this increases the likelihood of establishing a good latch (the correct sucking technique), preventing the need for correction later.[31] The newborn should remain with the mother throughout the recovery period, with procedures that interfere with breastfeeding or traumatize the infant kept to a minimum.[1,32] Rooming-in should be encouraged both in hospital and after discharge.[1,32]

All newborns should be nursed on demand.[1] Signs of hunger include increased alertness or activity, mouthing and rooting.[1] It is important to understand that crying is a late sign of hunger.[1] Newborns need to be nursed until satiety eight to twelve times within a 24-hour period, and should be roused to nurse if four hours have elapsed since the previous feeding.[1,23,32] At each feed the infant should be allowed to nurse at the first breast until satisfied, and then be offered the second.[23]

Several task forces have devised recommendations to increase the success rates of breastfeeding. Research recommends that no supplements (water, formula, etc.) be given to newborn infants unless medically indicated, and bottles (with expressed milk) and pacifiers be avoided until breastfeeding is well established, if used at all.[1,32,43] Infants require only breastmilk (i.e., no other nutrition) for approximately the first six months of life.[1] Breastfeeding should continue for at least the first twelve months, or longer if mutually desired.[1] If a mother chooses to wean before twelve months the infant should receive iron-fortified infant formula (not cow's milk) until one year of age.[1, 44] Iron-enriched foods should accompany the breast milk diet during the second half of the first year.[1]

New mothers need to be made aware of the breastfeeding support that is available in their community, before they leave hospital. It is also recommended that all women have a follow-up home visit with a health nurse or lactation consultant within 48 to 72 hours after discharge.[1,23] The primary care physician should see all newborns at three to five days of age.[1,23] An assessment of general health and infant weight should be accompanied by an evaluation for evidence of successful breastfeeding. The newborn should be assessed for adequate hydration, urination (six per day) and elimination (three to four stools per day), and should be assessed for jaundice.[1] The topic of breastfeeding should be supported at each well baby visit, and women should be advised to return to their physicians for a complete breast examination once breastfeeding has been terminated.[1]

TROUBLE-SHOOTING

Breastfeeding can be effortless and enjoyable for some, and a difficult struggle for others. It is important to have the skills and knowledge necessary to deal with the difficult situations that may arise. Most problems occur within the first six weeks, and with perseverance, most infants and women become very proficient at it.[35]

Slow Weight Gain

In an otherwise healthy newborn, the most likely cause of slow weight gain is insufficient milk intake.[34-35] A poor latch is likely the underlying problem and needs to be evaluated and corrected.[33-35] Nursing the infant more frequently (at least eight times within 24 hours) may also help.[23] No additional supplements (formula, juice, water, etc.) should be recommended.[34-35] The infant and mother should be followed carefully until successful breastfeeding has been established. Note that it is essential to rule out any organic cause of slow weight gain before assuming inadequate intake.[23]

Inadequate Milk Supply

Breastfeeding works on supply and demand.[23] More frequent nursing almost always increases the milk supply sufficiently.[23] Using a breast pump immediately after a feed may also be helpful in bolstering the milk supply.

Nipple Soreness

Breastfeeding should not be painful, yet nipple soreness is common and the most likely cause of early breastfeeding failure.[33-35] Nipples can become sore, cracked, and may bleed. The most common cause is a poor latch.[34-35] New mothers tend to endure the pain of a faulty latch because the infant appears to be feeding well. Appropriate treatment should be based on educating the mother and facilitating healing.[34-35] Women need to be reassured that the nipples will adapt to the nursing experience naturally, but that efforts can be made to ease the discomfort (table 1).

Candida Albicans

Candida has been called the hidden deterrent to breastfeeding and is likely an underdiagnosed cause of early weaning.[45] Persistently red and sore nipples after the first two weeks of breastfeeding should raise a red flag and make the health care professional think about Candida. [45] Candida albicans is a normal fungal organism found in the flora of mouth, skin, intestinal tract, and vagina. However, when present in increased amounts, it can cause oral thrush (and therefore nipple thrush) and be a tremendous source of discomfort for both mother and infant.[45] Thrush has several classic symptoms (table 2) but patients can be asymptomatic.[45] The most likely route of infection is vaginal delivery.[45] Therefore, the most effective treatment is prevention, by treating pregnant women with yeast infections during their third trimester. Lactating women should be made aware of the symptoms of thrush so they can seek medical attention. Treatment includes antifungal treatment for mother and infant, with mandatory follow-up.[45] Frequent hand washing, using disposable nursing pads, washing bras daily and sterilizing breast pumps, pacifiers, bottles and toys for 20 minutes helps to prevent reinfection.[45]

Table 1. Treating Nipple Discomfort

Check position and assure that infant has a good latch
Manually express some milk before feeding to soften breast
Apply warm compresses before nursing
Begin nursing on the least sore side
Allow breast milk to air dry on nipple area after feeding
Leave nipples exposed to air
Avoid nipple shields
Do not allow infant to fall asleep at the breast
Use Lansinoh® if ointment is used
Avoid soaps and drying agents

Table 2. Signs and Symptoms of Thrush

Mother:
Red nipples and areola
Nipple itching
Persistent sore nipples
Burning/shooting pain in breast during and/or after feeding
Cracked nipples that do not heal
White patches
Infant:
White patches on oral mucosa and tongue
Diaper rash
Refuses to nurse, or pulls away repeatedly during nursing
Slow weight gain
Gas
Fussiness
Recent antibiotic use

Breast Engorgement

Nursing mothers will likely experience discomfort due to engorgement at some time. They should be reassured that because their milk supply is driven by demand, the breasts usually adjust quickly. Comforting measures include: warm compresses, nursing frequently, varying nursing positions, initiating let-down before feedings, and massage the breast toward the nipple before and during nursing. For severe breast fullness, a good quality breast pump can be used after nursing followed by cold compresses.

Mastitis

While mastitis is not nearly as common as it once was, it can still be a result of early weaning.[23] Mastitis usually presents with sudden, intense, unilateral pain and flu-like symptoms.[23] A lobe of the breast is usually red, hot and swollen, and the patient is febrile.[23] The patient should be advised to continue to nurse on both breasts, but to begin each feed on the affected side.[23] The affected breast needs

to be emptied thoroughly at each feed by nursing or pumping.[23] Bed rest is mandatory.[23] An antibiotic that can be tolerated by infant and mother should be prescribed, with a course of at least 10 to 14 days.[23] Ice packs or warm packs can be applied for local relief, and acetaminophen can be taken for pain.[23]

CONCLUSION

The health and social benefits of breastfeeding are now well established in the scientific literature. Breast milk provides the ultimate nutrition for infants with the best health, developmental, and psychosocial outcomes. It is our job as health care professionals to become knowledgeable and skilled in the clinical management of breastfeeding in order to become enthusiastic breastfeeding advocates for our patients.

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RESTORATION OF SELF THROUGH RECONSTRUCTION OF FORM:

A Conceptual Review of Breast Reconstruction for the Postmastectomy Patient

By Mason S. Ross, MEDS 2001

INTRODUCTION

Breast Cancer: Still a Major Health Concern

Despite ongoing research efforts and advances in oncologic therapy, carcinoma of the breast currently remains a major threat to women. (Figure 1.) It is estimated that 19,300 new cases will be diagnosed in Canada during 1998,[1] securing carcinoma of the breast as the female cancer with the greatest incidence, next to malignancies of the skin.[1,2] Of even greater concern is that 5,300 Canadian females will succumb to the disease by the year's end,[1] making it the second leading cause of cancer mortality (lung cancer being first).[1,2] Indeed, a female born in North America today has approximately a one in nine chance of developing a primary breast tumour during her lifetime.[3] But, in addition to the psychological devastation of living with the disease, coping with the physical results of surgical treatment often adds insult to injury. It should therefore not be surprising that breast cancer and its associated illness experience are firmly entrenched at the forefront of women's current healthcare concerns. Today, several approaches are available in the attempt to restore the body to normal form after disfiguring breast cancer surgery. However, essential for a more profound appreciation of breast reconstruction is an understanding of the treatment of breast malignancy, the significance of the breast to society, and the psychosocial consequences of the loss of a breast. This review explores these topics, and examines the surgical management options of breast reconstruction for the postmastectomy patient.

Relevant Highlights of Treatment for Carcinoma of the Breast

The TNM staging system by the American Joint Committee on Cancer classifies patients with breast cancer into different groups based on prognostic criteria. Information regarding the size and invasiveness of the primary tumour (T), regional lymph node involvement (N), and existence of distant metastasis (M) determine what stage grouping is appropriate.[2] Stages are classified from I to IV, increasing according to the severity of disease.

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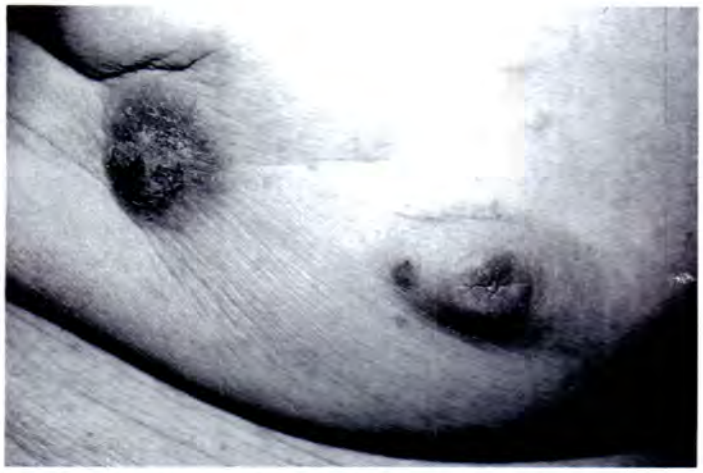

Figure 1. Carcinoma of the breast. This case is taken from 1976 to illustrate an advanced tumour. Today, it is much less likely to see breast cancer present in this manner.

Tumour excision is an integral part of managing carcinoma of the breast. Surgical procedures include either total mastectomy (resection of entire breast) or lumpectomy (removal of cancerous tissue with pathologically negative margins). Although the role of surgery is better documented for patients with early stage disease,[4] where complete tumour excision is more probable, total mastectomy with adjuvant radiation and chemotherapy may be of therapeutic benefit for patients with late stage disease as well.[5]

Although lumpectomy offers a superior cosmetic result when compared to mastectomy, initial concerns were that the procedure might not be as effective because of the decrease in tissue removal, and hence the decrease in probability of removing all malignant cells.[4] However, numerous studies indicate that breast conserving surgery results in similar survival rates when compared to mastectomy.[6,7,8,9] The medical community now generally believes that, in properly selected patients, lumpectomy is the appropriate surgical course of action.[4] Nevertheless, at least one third of patients may not be acceptable candidates for the procedure.[4] Contraindications for lumpectomy include extensive primary tumours, inability to obtain pathologically negative margins, occurrence of multiple primary cancers, or the presence of a carcinoma so large that there is no cosmetic benefit when compared to mastectomy.[10] Today, despite the compelling evidence against the need for radical breast excision in many cases, women often choose mastectomy based on the perception

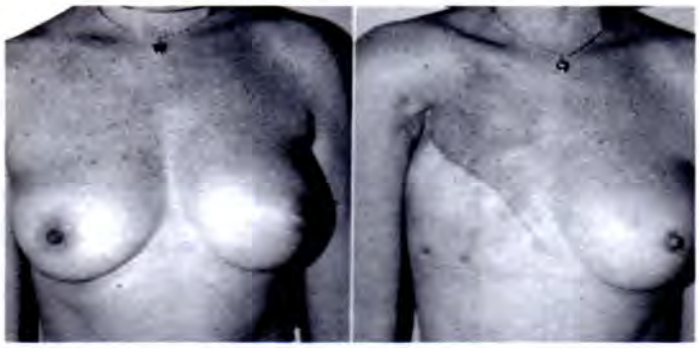

Figure 2. Before and after radical mastectomy.

of a more favourable prognosis. Although the frequency of lumpectomy is increasing, mastectomy remains the most often performed surgery for breast cancer.[2] (Figure 2.)

Significance of the Breast

The female breast has been a powerful symbol of femininity throughout history. It represents fertility, comfort, and sexuality[11] and is considered to be the most important marker of a woman's gender.[12] As such, many women have body image concerns after the amputation of a breast. The postmastectomy patient commonly feels mutilated and reports lower self-esteem.[13,14] She is likely to experience depression[12,14] and studies have shown that the majority of women report a decrease in desire for sexual intimacy, often resulting in the cessation of sexual intercourse.[13,15] Furthermore, the loss of a breast is often a disfiguring reminder of the cancer diagnosis which invokes fears of recurrence, adjuvant therapy, and most of all, death.[15] People more likely to suffer greater psychological trauma include single or younger women, patients who were critical of their breasts previous to mastectomy, and those whose self-esteem is primarily rooted in physical beauty.[12,14,16]

BREAST RECONSTRUCTION

Background

After mastectomy, women are typically extremely unsatisfied with the option of using an external prosthesis to simulate the breast mound. External prostheses do not improve body image,[17] and often serve to constantly remind women of their life threatening disease.[18] Consequently, there has been considerable interest in breast reconstruction. Top motivations reported by women to pursue breast reconstruction are to regain attractiveness, and to reclaim the sense of wholeness that they perceive the disease has taken away.[19] Often, reconstruction is perceived as an affirmation of the desire to keep living; a symbol of the commitment not to give in to the disease.[20] However, the surgical community was initially concerned over the possibility of worsening the prognosis of breast cancer through reconstruction; either via altered tumour biology or through increased risk of wound complications. They theorized that tumour biology might be altered by stimulating or masking cancer recurrence, or that the operation could weaken the immune system.[4] Also, an increase in wound complications could potentially delay adjuvant radiation or chemotherapy.[4] Fortunately, numerous studies have failed to show significant differences in tumor biology[21,22] or in wound complications[23,24] between patients undergoing mastectomy with reconstruction and mastectomy alone.

There are two main conceptual approaches to modern breast reconstruction. One involves silicone gel- or saline-filled prosthetic implants, and the other uses autogenous tissue flaps. Both methods have inherent advantages and disadvantages.

Implant-based reconstruction holds less short-term operative risk, but comes at a cosmetic and possibly a long-term price

The usefulness of implants is to replace lost breast volume. An implant placed deep to the pectoralis major muscle may be used immediately after mastectomy if adequate skin is available. However, if a skin sparing mastectomy does not occur, then tissue expansion is used to ensure adequate skin coverage for eventual accommodation of the prosthesis. The insertion of an implant or tissue expander typically takes less than one hour, and is hence an attractive form of reconstruction for the patient that has risk factors associated with surgery.[25] Despite that advantage however, implants carry a high failure rate due to infection, rupture, extrusion, or capsular contraction.[25] In addition, tissue expansion requires gradual inflation (4 to 6 months) of the soft-tissue mastectomy envelope to achieve a breast volume of about twice that of the contralateral breast. This commonly results in complaints of discomfort.[25] Subsequently, another operation is performed to remove the expander and insert the implant. Although attempts have been made to eliminate the need for two procedures by the use of combination devices, further revisions are often needed thereby invalidating the potential benefit from their usage.[25] In addition, tissue expansion requires many follow-up visits and, as such, may be more successful in the highly motivated patient.[26] Cosmetically, many surgeons feel silicone gel-filled implants provide a better approximation of breast tissue than the saline-filled type. When compared to silicone gel-filled implants, the shortcomings of saline-filled implants include a tendency for fullness or waviness in the superior half of the breast mound, and a decreased natural breast contour in the upright position.[27]

Controversy remains over whether the use of implants is connected to a wide variety of non-specific symptoms and deficiencies of immune system function. Although data do not currently indicate a causal relationship between implants and autoimmune disorders,[28,29,30,31,32] the lack of long-term data raises concerns for implant safety. In addition, little is known about the life span of implants beyond 20 years. For these reasons, many women continue to be anxious over the utilization of implants for reconstruction, and this should therefore be viewed as an additional disadvantage for their usage.[25] (Figure 3.)

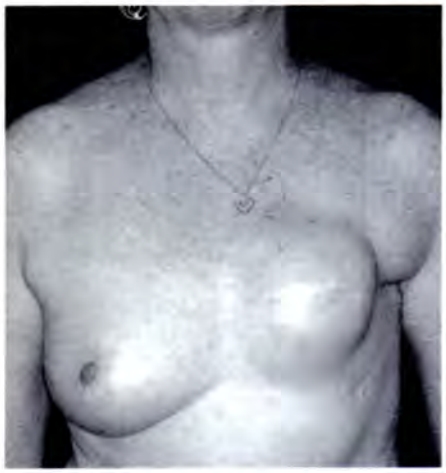

Figure 3. Implant-based reconstruction. Slight asymmetry is unnoticeable when the patient wears a brassiere.

Autogenous Tissue Reconstruction, Often the Procedure of Choice

Modern autogenous breast reconstruction is performed using myocutaneous flaps. The procedure involves the replacement of lost breast volume and skin envelope via the transfer of one's own muscle and skin layers from a suitable region that retain their original vasculature. The principal benefit of this type of procedure is the avoidance of the potential complications associated with foreign body implantation of internal prostheses. Since documentation of the use of latissimus dorsi myocutaneous flaps for breast reconstruction began over 20 years ago, many other flap transfer procedures have been described. Cosmetically, myocutaneous flaps better approximate the quality of breast tissue when compared to implants, resulting in more natural breast contour and improved symmetry with the contralateral breast.[27] Although this type of reconstruction is more complex and is associated with increased operative risk, autogenous reconstruction is more durable over the long-term than implantation.[25]

Today, the flap most commonly utilized for autogenous breast reconstruction is the transverse rectus abdominis myocutaneous (TRAM) flap.[33](Figure 4.) Specifically, the main advantages of the TRAM flap underlying its popularity are that the abdominal donor site is frequently of generous quantity to provide ample tissue for reconstruction, and that the patient often benefits cosmetically from an abdominal lipectomy at the same time. In addition, advances in microsurgery have successfully allowed free flaps (a flap detached from a donor site for microvascular anastomosis at the recipient site), such as the free TRAM flap, to be a common selection of autogenous breast reconstruction in many centres.[27]

Selection of Technique

Because of the tremendous variability of implant type, shape, and multiple adequate donor sites for autogenous procedures, there are numerous reconstructive possibilities, and as such, each case is unique. However, it is important to keep in mind that not every patient desires such a procedure, and therefore inadvertent coercion should be avoided. However, if interest in reconstruction is expressed, then the patient's health status is ascertained, and weighed against what is technically feasible as determined by body habitus.[26] Elderly women or patients with comorbid disease are best treated with less invasive procedures such as prosthetic implantation, possibly with tissue expansion as well.[4] Moreover, reconstruction with autogenous tissue is preferable in the otherwise healthy patient, if her body habitus is suitable.[4] When multiple options are appropriate, the patient may select the operative technique.[34]

Immediate versus Delayed Reconstruction

Historically, it was advised for the patient to delay reconstruction for a time after mastectomy to determine if the malignancy would return. However, this is no longer the case as numerous studies have concluded that immediate breast reconstruction is safe for selected patients.[21,22,35,36] In addition, it has been thought that a woman must live with the mastectomy defect for a time to appreciate her new breast. This view is not currently accepted either, since immediate breast reconstruction, when appropriate, has been shown to decrease the psychological trauma associated with mastectomy.[37] It is generally felt that patient selection for immediate reconstruction should be based on an understanding of the reconstructive options, stage of the carcinoma, amount of previous radiation therapy, and the surgical technique planned for mastectomy.[4]

Implant-based reconstruction, especially those involving tissue expansion, involves multiple office visits and can require subsequent revisions. Consequently, it is necessary for the woman to be well informed about her reconstructive options and be realistic regarding the outcomes of each, so that she may be better prepared for complications. In patients with advanced disease, where postmastectomy radiation of the chest wall is an integral part of therapy, a delayed reconstruction is indicated to avoid the risk of radiation necrosis in the newly constructed breast.[4] Radiation therapy before mastectomy

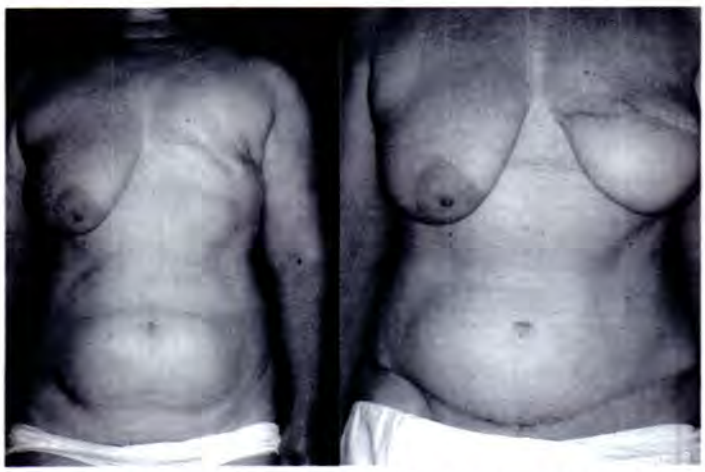

Figure 4. Before and after TRAM flap reconstruction. TRAM flaps often provide a generous amount of tissue for reconstruction.

may also hinder the reconstructive process by decreasing the probability that a local flap will take successfully, decreasing tissue elasticity, and affecting the viability of the pedicle of regional tissue reconstruction along with the vasculature needed for microsurgical reconstruction.[4] If the patient is at an increased operative risk due to prolonged anaesthesia, then a delayed reconstruction may also be appropriate.[13] Obese patients, smokers, and people with marked comorbidity such as diabetes mellitus, uncontrolled hypertension, and cardiovascular disease are also less ideal candidates for immediate reconstruction as they have an increased risk of developing complications.[38,39]

Reconstruction of the Nipple and Areola

Current methods of nipple reconstruction include either taking a composite graft from the contralateral nipple or using small local flaps to elevate tissue from the breast mound. Areolar reconstruction can be accomplished by grafting techniques or by tattooing. Nipple and areolar reconstruction can result in higher levels of patient satisfaction not achieved by improving physical contour alone.[40] (Figure 5.)

Psychological Outcomes

Most women feel positive about their reconstructive results. They often feel that the new breast represents a commitment to the future; a desire not to give in to the disease.[41] However, although improvements in technology and technique have enabled breast reconstructive results to be more aesthetically pleasing today than ever before, some women report disappointment that it did not return them to their premastectomy state.[42] To help overcome the risk of this potential distress, the patient should understand the purpose of reconstruction, and be realistic regarding her outcome. In light of this, it should be strongly encouraged that reconstruction not be presented as a cosmetic triumph, but rather as an aid to restore her to a sense of wholeness.

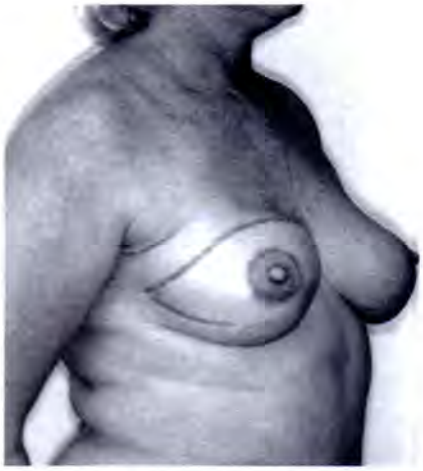

Figure 5. Reconstruction of the nipple and areola.

SUMMARY

As surgery often leaves women suffering from breast cancer disfigured and depressed, reconstructive procedures of the breast have evolved with the purpose of improving form. Reconstructive techniques typically involve implants or autogenous tissue flaps, and the choice of method depends on factors including overall health, body habitus, and patient preference. In the otherwise healthy patient, autogenous reconstruction is generally preferred because of the decrease in complication risks and concerns associated with implant-based reconstruction, often providing a cosmetically superior result as well. Presuming realistic patient expectations, psychological outcomes of breast reconstruction will tend to be extremely positive, showing that reconstruction of form in the postmastectomy patient can play a major role in a woman's psychological recovery.

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THE ROLE OF ULTRASOUND IN THE MANAGEMENT OF BREAST CANCER

By Jonathan Abele, MEDS 1999

Introduction

Breast cancer is the most common malignancy affecting women in Canada, and currently is the second leading cause of cancer-related female death. The expected incidence per annum in Canada is approximately 18,500, with approximately 5,000 expected deaths.[1] As such, it is an illness of significant proportion. While the prevalence of this disease is great, survival has been improving in recent years. This trend is thought to be due to a combination of both improved diagnosis and treatment.

A key improvement in the diagnosis of breast cancer has been the recognition of the importance of imaging modalities in screening. More specifically, numerous studies have provided clear evidence that regular mammography in conjunction with careful physical examination can significantly decrease mortality due to breast cancer. In fact, the combined data show a reduction in mortality of at least 30%.[2] This information lead to the development of the Ontario Breast Screening Program in the late 1980's. Current Canadian screening guidelines include mammography at least every two years for all women age 50-69. Regular mammography is also recommended for those age 40-49 in high risk groups such as those that have had a previous breast cancer or those with a family history of breast cancer in first degree relatives.[3]

Mammography has thus been established as an important imaging modality for breast cancer both experimentally and clinically. Because of its success in reducing mortality, an obvious question arises as to the role of other imaging modalities in the management of breast cancer. One modality which has been extensively investigated is ultrasound.

In fact, there are multiple reasons why the breast may be the most ideal organ in the human body for examination by ultrasound. Its relatively small size allows examination with high-frequency, high-definition probes. Also, air and bone which can interfere with sonography are not present in the breast. Finally, there is sufficient variance in the sonic impedences of the tissues in the breast that one can use this modality to differentiate glandular tissue, fat, fascia, lymph nodes, and normal sized ducts from one another.[4] Ultrasound can demonstrate the skin, subcutaneous fat, breast parenchyma, retromammary fat, pectoralis muscle, ribs, and anterior chest wall.[5] An advantage of ultrasound is the capability for real-time scanning of the breast. This quality is important in correlating images with physical findings, as well as in biopsy and interventional techniques.[6] Ultrasound also does not share the significant albeit small radiation risk associated with x-ray use in mammography. As a result of these characteristics, ultrasound has become established as an important imaging adjunct in the diagnosis and management of breast disease.

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Is there a role for ultrasound in screening for breast cancer?

For ultrasound to be considered a useful imaging tool for primary screening of breast cancer, it must display an efficacy equal to or greater than the current mammography program. At this point, there is no research available to support such an efficacy.[5,7,8] Ultrasound simply does not detect all cancers that are visible mammographically.[8] Studies with high frequency, real-time equipment in examination of known breast cancers have shown false negative rates for ultrasound ranging from 0.3% to 47% (mean 20.7%).[8] There are a number of reasons for this. Firstly, a significant number of breast cancers are isoechoic with fat or breast tissue, and thus difficult or impossible to visualize sonographically.[5] Secondly, ultrasound has poorer resolution than mammography for solid lesions. Ultrasound cannot reliably detect solid lesions <1 cm in diameter.[7] In fact, in one study of 12 cancers <1 cm, ultrasound failed to detect 11(92%).[5] Finally, microcalcifications are not consistently visible sonographically.[7,9] Mammography, however, can consistently detect suspicious microcalcifications regardless of location. Many of these microcalcifications can be <0.5mm in diameter.[10] Mammography is better in both resolution and contrast, and thus is a better screening tool.

While mammography is the accepted imaging modality for breast cancer screening, ultrasound may yet have a role. Recently, there have been a few retrospective reports of malignant breast masses being initially detected only by ultrasound after negative high-quality mammograms and negative clinical examination.[5] For example, Gordon and Goldenberg at UBC reviewed 12,706 cases of breast ultrasound performed between 1989 and 1994 for evaluation of a palpable abnormality or a nonpalpable, mammographically detected mass.[11] Of these cases, 1575 "sonographically incidental" masses were detected that had not been palpable nor seen on mammography. Of these incidental masses, 44 (2.8%) were surgically confirmed as malignant. A recent prospective study presented by Kolb et al. at the Radiological Society of North America Meeting in

October, 1996 examined 2,300 women with radiographically dense breasts, negative findings on mammography, and a negative clinical examination.[5] Ultrasound on these women revealed a breast cancer detection rate of 4 per 1000. This is a significant rate for a screened population.

In summary, combined evidence shows that ultrasound alone is an inadequate imaging modality in comparison to mammography in the role of primary screening for breast cancer. The main reasons include the inability to depict microcalcifications, difficulty in imaging fatty breast, inability to differentiate benign from malignant solid masses, and unreliable depiction of solid masses smaller than 1cm.[7] Evidence has shown, however, there may be a role as a secondary screening technique in high-risk women. These include those women with a strong family history of breast cancer, those with a personal history of breast cancer, or those with suboptimal mammography.[5] Further prospective research is needed to better clarify this role.

What is the role of ultrasound in the diagnosis of breast disease?

The primary and most important role for ultrasound in evaluating breast disease is the differentiation of the cystic vs. solid nature of a mass found by either palpation or mammography (Figure 1).[5,7,8,9] This differentiation reduces the need and therefore the trauma and cost of surgical biopsies. The significance of this is revealed in that more than 500,000 benign breast biopsies are performed per annum in the USA.[12] It is not unreasonable to assume a similar relative prevalence in Canada. Ultrasound is reported to be 95-100% accurate in diagnosing a lesion as a cyst if all criteria are strictly met.[5] These criteria include a lesion which on ultrasound has no internal echoes, smooth and sharp margins, and a round or oval shape. Reactive shadowing at the edges and posterior acoustic enhancement may also be present. If these criteria are met on assessment of a mass, most radiologists would consider it diagnostic.[5,7,8] Sonographic signs suspicious for malignancy include a hypoechoic mass and margin irregularity. It is important that for any suspicious solid lesion, or any lesion not strictly following the classic cyst pattern on ultrasound, a biopsy must be considered to confirm a diagnosis.[12]

This capability is even more valuable in the evaluation of a palpable breast mass in a woman younger than 30. These women are not regularly screened by mammography and have an extremely rare incidence of breast cancer. They are also more sensitive to radiation than older women. For these reasons, many recommend ultrasound as the primary imaging modality for palpable masses in this age group.7,8 If the mass is a cyst, no further evaluation is required. If not, then one would obtain a mammogram and then a biopsy. While ultrasound has a unique role for this age group, it should be stressed that for women older than 30, it is recommended to begin imaging with mammography, using ultrasound as an adjunct when indicated.

A second diagnostic indication for ultrasound is in the investigation of women where mammographic sensitivity is low. These conditions include radiographically dense breasts, near prostheses, at the breast periphery in rare cases of mammographic inaccessibility, in surgically altered breasts, or in the breasts of pregnant or lactating women. Ultrasound is not an alternative to mammographic screening of these women, but is an adjunct to be used when mammography is contraindicated or of unacceptable quality.[5,7,8]

A third major role for ultrasound in diagnosis is as a guidance mechanism for interventional procedures.[13,14] Classically, open surgical biopsy has been the gold standard for the diagnosis of a breast lesion. This can be costly and traumatic as the standard of care has been lesion removal by lumpectomy to both diagnose and provide definitive treatment concurrently. More recently, surgical intervention to this extent has been widely replaced by fine needle aspiration (FNA) or core needle biopsy (CNB), so as to reduce trauma for benign disease. While the efficacy of these procedures compared to surgical biopsy has never been studied in a randomly controlled trial, a retrospective study has reported false negative rates as low as 0.04%.[14] For readily palpable lesions, these procedures can be guided by physical exam.

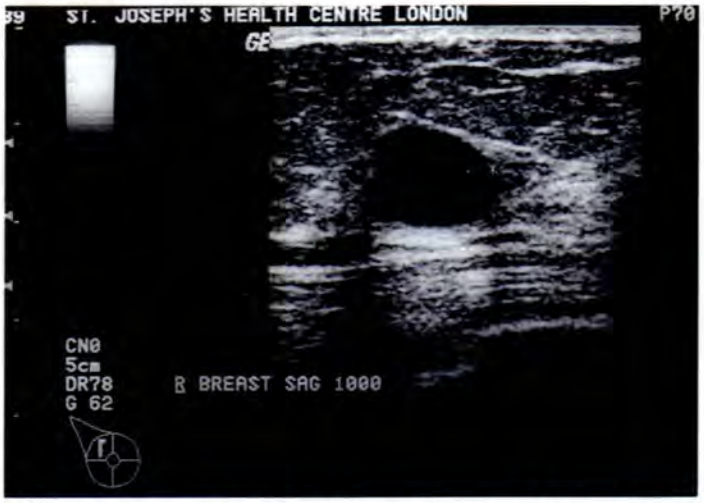

Figure 1a: An example of a simple cyst diagnosed through breast ultrasound

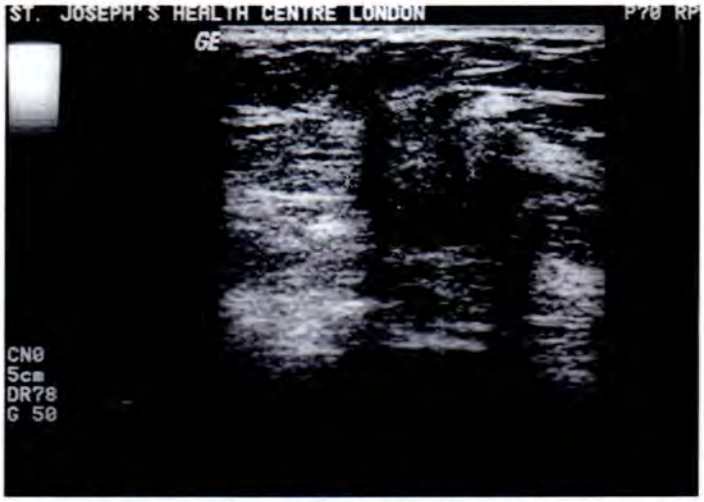

Figure 1b: A solid mass proven to be malignant by ultrasound-guided core biopsy

For non-palpable lesions discovered through mammography, however, imaging guidance is imperative. As well as ultrasound, needle biopsies have been successfully guided via mammography, CT, MRI, and nuclear medicine studies. The efficacy of FNA and CNB appears to be independent of the imaging guidance system if properly done.[14] Ultrasound, however, has the advantages of being relatively cheap, atraumatic, and real-time. It is currently a favored modality.[13,15]

What is the role of ultrasound in therapy for breast disease?

While ultrasound is primarily a diagnostic modality, it does have some therapeutic indications. Ultrasound-guided cyst aspiration is performed not only for diagnostic purposes, but is also indicated for the relief of symptoms such as pain.[14] The real-time nature of ultrasound is beneficial for these indications as one can visualize cyst reduction.[9] Similarily, ultrasound can be utilized for the therapeutic drainage of an abcess.[9]

For solid masses, definitive treatment most often involves surgery. Ultrasound plays a useful role in imaging the pre-operative needle localization of a malignancy.[8] By using the pre-placed needle as a guide, the surgeon can then confidently excise the mass with minimal trauma and disfigurement. This procedure is especially useful for non-palpable masses.

What is the future of ultrasound in the management of breast cancer?

With technological development and increasing resolution ultrasound may eventually have a role in breast screening as previously described. While it is unlikely to ever replace mammography for primary screening, it may eventually be a suggested adjunct for more efficacious screening programs.

Better technology may also enable better differentiation between solid masses. While ultrasound at present is excellent in differentiating cystic from solid lesions, it is not yet acceptable in distinguishing benign from malignant states. Some authors have described different characteristics of a solid mass which suggest malignant vs. benign pathology.[16] Malignant characteristics include spiculation, angular margins, marked hypoechogenicity, shadowing, calcification, duct extension, a branching pattern, and microlobulation. More benign patterns include an absence of these malignant findings, intense hyperechogenicity, an ellipsoid shape, gentle bi- or trilobulations, and a thin, echogenic pseudocapsule. Stavros *et al.* go on retrospectively to say that for solid masses with classic benign characteristics on ultrasound the negative predictive value is over 99%.16 Furthermore, they state that these cases can be managed with close follow-up imaging rather than biopsy. It is important to note that there are no prospective data to support this statement.[5] The current standard of care is to biopsy any non-cystic lesion, at least via FNA, to obtain a more accurate tissue diagnosis. This information does, however, raise the possibility that perhaps with improved technology and further research, ultrasound may account for a vast reduction in the number of unnecessary biopsies.

Doppler ultrasound is another technology that may develop further. The rationale for its use is the fact that many cancers appear to have far greater blood flow through neovascularization than do benign lesions. In one study, Cosgrove *et al.* state that 96% of benign breast changes had no color Doppler signals. They state that vessels were detected in 57 of 58 cancers.[17] According to their study, one could conclude that "color Doppler signals in a lesion otherwise thought to be benign should prompt a biopsy, while the absence of signals in an indeterminate lesion is reassuring" [17]. While this conclusion has little clinical implication at present, it does suggest that with future technology Doppler may have a role in differentiating benign from malignant lesions.

Conclusion

Currently, mammography is the imaging modality most widely associated with the management of breast cancer. Ultrasound is an adjunctive modality which also should be considered. While at present it has little value in screening for breast cancer, it does have value in other roles. Diagnostically, its most important uses include differentiating cystic from solid lesions, as well as in guiding fine needle aspiration and core needle biopsy. Therapeutically, ultrasound is useful in cyst drainage and in needle localization of non-palpable masses for surgery. Due to its many attractive features, further technological development may expand the role of ultrasound, and ultimately improve the management of this prevalent and serious disease.

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THE CLINICAL BREAST EXAMINATION

By Briar Sexton, MEDS 2000

INTRODUCTION

As a third year medical student given the task of performing a full physical exam on a female patient over the age of 55, it struck me that a "full physical" excluded a clinical breast exam. This prompted an investigation into medical student training in Clinical Breast Exam (CBE) skills, which suggested that the breast examination does not receive sufficient emphasis in the current curriculum and that more effective ways of teaching it could be employed.

My research includes a review of literature concerning the importance of the Clinical Breast Exam and the most effective ways of teaching it and of ensuring it is performed on all eligible patients. As well, I conducted a brief survey of the UWO Medical School Class of 2000 three weeks prior to the commencement of their clerkship in order to assess their level of training and degree of skill and comfort with respect to the CBE. As the pelvic and rectal exams are also excluded from "full physical exams" I asked students to exclude these exams when comparing the CBE to other components of the physical exam. One of the main purposes of the survey was to determine if the increased number of times students performed other clinical skills as well as the increased opportunity for observation and feedback would make the students feel more comfortable and proficient with them. A skill such as auscultation of the heart is performed on virtually every patient seen in the Phase II or second-year Clinical Methods Curriculum. It may be unreasonable to attempt this level of exposure to the CBE as it is more invasive of patient privacy, however, this in itself argues for ensuring the CBE is emphasized in the curriculum in other ways.

At the University of Western Ontario Faculty of Medicine, pre-clerkship training on the clinical breast exam consists of one three hour self-learning session using a model of a female breast. There is no formal training on patients, either actual or standardized. Students may reach their clerkship without having performed a CBE. The literature clearly demonstrates that this training is not sufficient. A retrospective analysis using clinical clerks at two different US medical schools showed that over 50% of students had not had a single CBE supervised during the course of their clerkship.[10]

RELEVANCE OF THE CLINICAL BREAST EXAM

Breast cancer is the most common malignancy and the second leading cause of death among Canadian women over the age of 55. Breast cancer accounts for 30% of all new cancers in Canadian women.[1] While both genetic and environmental factors have been implicated as etiologic factors, the cause remains unknown.

Breast cancer screening consists of a three-tiered strategy which includes breast self-exam (BSE) by the patient and clinical breast exam (CBE) and imaging of the breast through either ultrasound or mammography by the physician. Current screening recommendations are for women between ages 50-69 to perform a monthly breast self-exam and to receive a yearly clinical breast exam and a bi-annual mammogram.[2] The importance of physicians performing a clinical breast exam in addition to mammography has been underscored in a study of the two modalities' sensitivity for cancer detection. The sensitivity for cancer detection is 24% with CBE alone and 62% with mammography alone while the sensitivity of the two methods combined is 75%.[3] Furthermore, women may learn how to perform a self-exam of the breast by watching their physician. Alternately, having the physician perform the exam may underscore to them the importance of palpating the breast and thus encourage them to monitor their breasts monthly.

Data in both Canada and the United States suggest that physicians and students are not following the current screening recommendations.[4] In fact, the number of women who report having a CBE at their annual physical is decreasing.[5] Studies investigating why physicians do not perform clinical breast exams on all eligible patients frequently cite a lack of physician comfort and skill as the causal factor.[5,10,11] A study of 398 physicians in Minnesota found that less than one third of them reported their skill at performing a CBE as excellent and less than half of them described themselves as "very comfortable" performing the exam. Also of note was that in comparison to their male counterparts, female physicians were more comfortable and more likely to assess their skills as excellent in numbers which reached statistical significance.[5] Another study by the same authours found that in addition to being more comfortable performing a CBE, female physicians also performed the exam on more eligible patients than their male counterparts.[6] This echoes the results of another study which documented that patients of female physicians were significantly more likely to be screened by a clinical breast exam than patients of male physicians and that neither group screened all eligible women.[3] From this data, the lesson can be drawn that first, there is a deficit in screening with CBE. Second, physicians are less likely to perform CBE if they are uncomfortable performing the skill. Third, the reasons why female physicians are more comfortable with and more likely to perform a CBE must be elicited in the hope of eliminating this gender disparity.

Unfortunately the trend of decreased screening numbers and gender disparity in physician comfort level exists at the student level as well. For example, a retrospective chart review of 111 women eligible for CBE seen by internal medicine residents at George Washington University Medical Centre showed that only 35 of them received a clinical breast exam.[7] An assessment of primary

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care residents from seven training program noted performance deficiencies in breast examination skills and lump detection sensitivity. There were significant differences in the performance abilities of residents from different training programs. The programs with poorer performance in Clinical Breast Exam were also the programs where the CBE was not emphasized in the curriculum and the residents described the training they received as "poor to fair".[8]

A survey of students currently entering their clinical clerkship at UWO posed the question "Relative to other clinical skills (but excluding pap and rectal exam) how adequate is the instruction you have received through the Clinical Methods Curriculum?" Students were asked to rate it as "Excellent, Good, Fair or Poor" Of 57 respondents, 50 (89%) considered it "Poor", 6 considered it "Fair" and 1 considered it "Good". A second question posed was "Relative to other clinical skills (but excluding pap and rectal exam) how comfortable/relaxed do you feel performing a clinical breast exam?" Of 57 respondents, 36 answered "Poor" and 14 answered "Fair". Only 6 students answered either "Good" (n=4) or "Excellent" (n=2). In response to the question "Relative to other clinical skills (but excluding pap and rectal exam) how confident do you feel about your ability to detect a breast pathology by performing the CBE?" 38 respondents said "Poor" and 16 said "Fair" and 3 said "Good". No students felt their ability to detect pathology was "Excellent" relative to their other clinical skills. This data argues strongly for placing greater curriculum emphasis on the CBE.

TEACHING THE CLINICAL BREAST EXAM

The most effective way to teach current and future practitioners the CBE and to ensure they perform it on all eligible patients has been addressed in a number of studies with success. The medical school curriculum at the University of Western Ontario could benefit greatly by adapting successful strategies for teaching clinical breast exam. The outcome would be more competent and comfortable future physicians.

A compelling argument can be made that to improve both the level of comfort and skill of medical students in performing CBE need not be a time-consuming measure. The impact of even one training session or intervention to teach Clinical Breast Exam has been documented in several studies. A study that used an office-based training program targeted at primary care physicians improved their ability to correctly detect lumps in a silicone breast model. The mean number of correct lump detections in a model with 5 lumps increased from .66 before to 3.2 after instruction and the improvement was sustained at a six month follow-up.

Utilizing standardized patients is an alternative method by which some schools teach the CBE. A study conducted using medical students compared the performance of a control and experimental group. Both groups received "traditional" instruction consisting of a thirty minute videotape on the breast exam and assigned readings immediately prior to commencing their clinical clerkship. In addition, the experimental group received a single 70 minute teaching program run by Standardized Patients (SP's) in which they performed a CBE, received feedback and then practiced the CBE on the Standardized Patient while receiving ongoing feedback. The experimental group scored significantly for both skill level and professionalism at an OSCE station for CBE in a follow-up at the end of the twelve month clerkship.[10]

CONCLUSION

The conclusions to be drawn from this are clear. The Clinical Breast Exam is a necessary part of women's healthcare which should be performed on all women according to current screening recommendations. There exists among both current and future physicians a phenomenon of sub-optimal screening rates, skill level and comfort level. This has been documented at UWO by a student self-assessment survey. Interventions to teach the CBE can be simple and effective and thus curriculum modification need not be extensive. It could mean replacing the three hour self-learning session with a supervised viewing of the video followed by supervision of the CBE on the current model breast. Alternately, access could be provided to the more sophisticated breast models employed in the Breast Cancer Clinic. It may even be possible to arrange for students to attend a pre-operative clinic for women with carcinoma of the breast. As a responsive and responsible medical school, the University of Western Ontario should strive to address any and all curriculum deficits. It is in the interest of women's health and physician competence to enlarge the role of CBE in the pre-clerkship curriculum.

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THE LINK BETWEEN ORAL CONTRACEPTIVE USE AND BREAST CANCER

By Fiona O'Sullivan, MEDS 2002

INTRODUCTION

Breast cancer is a serious, prevalent disease affecting women around the world. This is a health issue of particular interest to researchers, since the incidence of breast cancer in women has been increasing.[1] A number of researchers have investigated the possible link between estrogen and the pathogenesis of breast cancer. More specifically, research has been conducted to investigate the relationship between oral contraceptive use and breast cancer in women. This article is a review of recent research on this topic.

ESTROGEN AND BREAST CANCER

It has been well established that hormones such as estrogen play key roles in the development of breast cancer.[1] It is thought that these hormones increase risk of breast cancer via effects on cell division in breast epithelium. Research suggests that "the cumulative frequency of ovulatory cycles is a primary determinant of breast cancer risk."[1] For instance, it has been found that women with breast cancer tend to have shorter menstrual cycles, earlier age of regular menstrual cycles, and later age of menopause, than controls.[1] There is also substantial laboratory evidence that suggests that estrogen is related to breast cancer risk. For instance, mice and rats exposed to exogenous estrogens have increased incidence of mammary tumours.[1] In humans, breast cancer patients have been found to have up to four times as much free estriol as controls.

Overall, there is strong evidence of a link between estrogen exposure and breast cancer. Since such a link has been established, there is reason to believe that oral contraceptives, or other exogenous estrogens, may increase one's risk of breast cancer.[1] This is an important area of investigation, since a number of women use oral contraceptives.[2] This leads to the next section, which will review the research findings to date on the relationship between oral contraceptives and breast cancer.

ORAL CONTRACEPTIVE USE AND BREAST CANCER

In a review of research on oral contraceptive (OC) use and breast cancer, it is reported that the majority of epidemiological research that was published prior to 1984 did not find evidence of OC use related to increased risk of breast cancer.[3] However, since 1984 there have been a number of studies that suggest that some sub-groups of women who use OCs have an increased risk of breast cancer, along with several studies finding no such association, resulting in contradictory, and difficult-to-interpret findings.

When studying women who have ever versus never used OCs, research has failed to find a relationship between ever use of OCs and breast cancer risk.[3] A group of researchers have suggested that "ever" use of OCs is likely too crude of a measure to reveal a link, if one exists.[3] They suggest that researchers consider sub-groups within OC users, since positive links between OC use and breast cancer are more often found in studies which focus on particular subgroups of women. For instance, most of the studies that have investigated OC use in women diagnosed with breast cancer at a young age (under age 45) have found that OC use does increase the risk in this subset of women.[3] In a meta-analysis of such studies, researchers found an overall RR of 1.5 for young women in one review of research, [4] and a summary RR value of 1.4 was found in another review. [5] Also, it appears that long duration of OC use before full term pregnancy is associated with increased risk of breast cancer, with summary risk estimates being 1.7,[4] and 1.4.[5]

A prospective cohort study was recently conducted to investigate the breast cancer risk associated with OC use in a number of sub-groups of women.[6] This study involved the Nurses' Health Study in the US, which included 114 880 women. Of these women, 3 383 had breast cancer. The researchers found a marginally significant increase in breast cancer risk in women who had last taken OCs within the past five years (RR = 1.20; 95%CI = 1.00 - 1.44). As the authors reported elsewhere,[6] they also found increased risk of breast cancer associated with current OC use (RR = 1.53; 95%CI = 1.06 - 2.19). There was no relationship between breast cancer risk and OC use prior to first pregnancy, even when analyses only included the sub-groups of women by age and parity. Also, no relationship was found between duration of OC use and breast cancer.[6]

There are a number of strengths of this study. First of all, this has been the largest prospective study to date on this topic. Since the investigation was prospective in nature, there was little likelihood of selection or recall bias.[6] Secondly, the researchers controlled for many possible breast cancer risk factors in their analyses (e.g. age, BMI, age at menarche, etc.). In addition, the OC users and non-users in this study were similar on most of these risk factors. Finally, there were high follow-up rates of the

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study participants (at least 90%).[6]

A weakness of this study is that there was limited power in some analyses, since there were few cases in some of the sub-groups.[6] For instance, there were only six OC users with breast cancer in the 30-34 year age group, and 27 OC users with breast cancer in the 35-39 year age group. The limited power here may explain why this study did not confirm other studies' findings that OC users under the age of 45 are at increased risk of breast cancer.[6] The studies that found such a relationship tended to be case-control studies, which had more cases, and thus increased power.

In summary, these investigators found that current and recent OC use is associated with increased risk of breast cancer, a finding that has also been reported in reviews and meta-analyses.[6] They did not find any increases in breast cancer risk due to long OC use, or OC use prior to first pregnancy, which is also consistent with other recent studies. Finally, their one finding that was not consistent with other research findings (lack of increased risk for OC users under age 45) should be interpreted with caution, since there was limited statistical power for this particular analysis. Overall, the findings of this study were consistent with the view that any relationship that may exist between breast cancer and OC use is a short-term effect only.

A large case-control study that was conducted fairly recently found relationships that were consistent with the findings of the previously discussed study.[6] This was a population-based case-control study, with 6751 cases and 9311 controls.[7] As with the previously discussed study, in this investigation a number of potential confounding variables were controlled. The researchers found that recent use of OCs (within past 5 years) for women aged 35-44 years was associated with increased breast cancer risk (RR = 2.0; 95%CI = 1.1 - 3.9). However, the authors did not find a relationship between breast cancer risk and: current use of OCs, age at first use of OCs, or long duration of OC use.[7]

Newcomb *et al's* case-control study has a number of strengths.[6] Firstly, they had more power than did Hankinson *et al*'s cohort study, 7 for they had twice as many cases. Secondly, they had high questionnaire response rates (80.7% for cases, and 84.2% for controls). Furthermore, their questionnaire was quite reliable, for when they retested it 6-12 months later, the Spearman correlation coefficients ranged from r = 0.89 to r = 0.98. Finally, they found that the recent cancer cases who were OC users in their study were less likely to have undergone mammography than the cases who were former users, which allowed them to rule out the possibility that their positive findings were due to increased surveillance in recent OC users.[7]

Overall, Newcomb *et al* found that recent OC users who were aged 35-44, and/or had low BMI, were at increased risk of breast cancer.[7] However, duration of use was not a risk factor. The researchers considered two possibilities for their findings of an increased breast cancer risk in recent OC users. Firstly, this finding could be merely due to the fact that young women are more likely to have used OCs recently, and they seem to be more prone to OC effects. Secondly, the results could suggest that OC effects on breast cancer risk are due to promotional effects on existing tumours, rather than due to triggering effects.[7]

In summary, research that was reviewed by Malone *et al* generally found that OC use for a long duration prior to first pregnancy increases a woman's risk of breast cancer.[3] However, two large studies since then have not corroborated these findings.[6,7] What has been found in most recent studies is that recent and/or current OC use is a risk factor for breast cancer.[6,7] This, combined with lack of evidence for a relationship between long-term OC use and breast cancer, suggest that OCs may play a small, short-term promotional effect on existing cancer tumours.[6,7]

CONCLUSION

There are a number of aspects of the research that are in support of a link between OC use and breast cancer. First of all, carcinogenic effects of OCs on the breast is biologically plausible, given experimental evidence. Secondly, prospective cohort studies and case-control studies have found a link between OC use and breast cancer. Thirdly, findings that OCs play a role in breast cancer is consistent with the descriptive epidemiology of cancer, since breast cancer incidence is increasing as OC use increases. However, there are a number of weaknesses with the research to date. First of all, the research in this area lacks consistency. Secondly, the strength of the association in studies with positive findings tends to be quite low. Finally, although the quality of research seems to have improved, recent research still lacks enough cases to have high enough statistical power for analyses of sub-groups. The only conclusion that can be made thus far is that OCs seem to have a small, promotional effect on breast cancer in some sub-groups of women, such as those who are young and are currently using OCs. There does not appear to be evidence of long-term effects of OC use on breast cancer risk.

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NAUSEA AND VOMITING IN PREGNANCY: A BRIEF REVIEW

By Tammy Clifford

INTRODUCTION

Nausea and vomiting during pregnancy (NVP), better known as "morning sickness," affects upwards of 50% of pregnancies.[1-11] It is thought to occur more frequently among nulliparous women in Western populations and tends to recur in subsequent pregnancies.[3,12,13] In the majority of these cases, NVP is clustered in the first trimester, but not necessarily during the morning hours.[7,9] Its occurrence is so pervasive that NVP is considered a hallmark of pregnancy. The experience of NVP may include fatigue, irritability and sleep disturbances. Although research has failed to produce definitive conclusions regarding the aetiology of NVP, many believe it to be a normal physiologic occurrence which results the sudden and substantial physiologic changes which characterize the first few weeks of pregnancy.[12] Often, NVP subsides, without residual effects, near the end of the first trimester.

In a small proportion of NVP cases, however, vomiting is so severe and prolonged that it interferes with the woman's fluid intake and nutrition. This can translate to significant weight loss (>5% of body weight) and electrolyte and acid-base imbalances which often bring about hospitalization.[3] The prevalence of this condition, known as hyperemesis gravidarum (HG), is estimated to range from 0.5 to 10 per 1000 pregnancies.[8,14,15] While some may dismiss NVP as not being a legitimate medical concern, research findings suggest that the experiences of NVP and HG affect the quality of women's lives. For example, data from a Swedish survey indicated that in 12% of pregnancies, NVP was so severe that it precluded continuous employment.[7] Alarmingly, data from the Motherisk program at the Hospital for Sick Children, corroborated by the findings of Jarnfelt-Samsioe, indicate that a significant number of women decide to terminate their pregnancies as a result of their experience with NVP and/or HG.[7,16] There are, however, many methodological issues regarding the Motherisk study which are deserving of mention. The first concern is how representative the study sample is of the general populace, as women who were enrolled as participants had voluntarily responded to advertisements placed in Canadian and American newspapers, magazines and electronic media. It could be that women who responded to the advertisement were motivated, for whatever reason, to share their story. Thus, these results may not generalize to the general population of pregnant women. Secondly, the study's retrospective design may have biased some findings, as women who elected to terminate their pregnancies may have been searching for a reason and, upon reflection, the experience of NVP was an easy reason to give. This is not to say that these results are untrue but that caution should be used when interpreting study results and that future works must address these methodological deficiencies in order to facilitate understanding of NVP. It is not doubted that, as researchers from the Motherisk program suggest, this finding is an "unacceptable combination."[16] It is evident, then, that much work remains to be done in order to improve our understanding of NVP and HG and to minimize its effects on the lives of pregnant women and those around them.

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DIAGNOSIS

Although NVP and HG can be thought to represent opposite ends of a continuum, both are diagnoses of exclusion; before establishing a diagnosis of NVP or HG, clinicians must first rule out other potential causes of nausea and/or vomiting, such as gastroenteritis, cholecystitis, peptic ulcer, food poisoning, etc. The experience of NVP is, undeniably, bothersome but is usually a self-limiting condition. On the other hand, the experience of HG can, if left untreated, be potentially life-threatening. Clinical features of HG include intractable vomiting which can lead to significant weight loss, severe disturbances of electrolytes , depletion of mineral stores, and hypovolemia. Laboratory findings indicate ketonuria, hyponatremia, hypokalemia, hypochloremia, metabolic alkalosis with paradoxical aciduria and elevations in urine specific gravity, hematocrit, and blood urea nitrogen.[6]

OUTCOMES

Substantial reductions in maternal mortality have been made over the past few decades, owing to improved understanding of the effects of HG and aggressive treatment strategies which aim to restore maternal fluid and electrolyte balances. Left untreated, complications of HG include Wernicke's encephalopathy,[17,18] coma, hepatorenal failure and death.

Historically, NVP was thought to be a positive predictor of pregnancy outcome, specifically with respect to birth weight and gestational age.[13,19] Recent findings uphold the suggestion that the experience of NVP is associated with a reduced risk of miscarriage, stillbirth, fetal mortality, preterm delivery, low birth weight, perinatal mortality or growth retardation.[7,9,20] The outcome of HG, however, is not so definitive. While most studies report no substantial deleterious effects of HG on maternal and fetal outcomes,[3,9,13,21-23] several studies report

associations between severe HG and negative outcomes such as fetal growth retardation, pre-eclampsia and small-for-gestational age births.[8,21,24-26] Other reports have hinted at an elevation in CNS and skeletal malformations in children whose mothers experienced HG.[8,21,26,27] It has also been suggested that maternal ketonemia, whether due to HG or a metabolic disorder, adversely affects the neuropsychological development of the infant.[28,29] It is important to note, however, that the limitations associated with the designs of these studies make it impossible to infer a causal relationship. Additionally, it is expected that prompt and appropriate treatment to address maternal weight loss and electrolyte imbalances will reduce the likelihood of adverse outcomes.[2]

AETIOLOGY

In keeping with the established trend of uncertainty and despite concerted research efforts over the past few decades, the exact mechanisms underlying NVP and HG are still unknown. Recently proposed mechanisms include *Helicobacter pylori* infection,[30] vitamin B deficiency,[31,32] endocrine imbalances,[33-36] alterations in serum steroid hormone levels,[11,26,37-39] and psychological disturbances.[3,40-50] While each of these hypotheses has been studied clinically, none has been proven definitively.

For example, an association between HG and human chorionic gonadotropin (hCG) is plausible, given that the incidence of HG in pregnancies of multiple gestation is elevated, as is the concentration of hCG. The fact that the onset of HG corresponds to the time at which hCG levels reach their peak lends further support to this hypothesis. Research findings, however, have been contradictory, weakening the possibility of a causal association.[3,11,38,51-55] In terms of psychology, some researchers have suggested the NVP and HG may stem from a "protest" reaction against the pregnancy and/or attempts by the woman to elicit attention and sympathy from family and friends while addressing hostility toward the father of the baby.[40,41,48] The absence of definitive research findings, despite concerted efforts, may be attributable, in part, to a failure to see NVP and HG as manifestations of an interplay of biological, psychological and social factors. Additionally, most studies have examined nausea and vomiting as a single entity. This could introduce bias into the research, particularly in retrospective works, since nausea, as a subjective entity, is more difficult to recall than vomiting. Future research must address these limitations and utilize sound study designs if our understanding of these conditions of pregnancy is to improve.

TREATMENT

The management of NVP in mildly symptomatic women typically involves reassurance, dietary modifications and, in some cases, drug therapy. Pharmacological measures may need to be considered for the treatment of women whose NVP continues, even after receiving reassurances and after modifying her diet.[1,2,16] In light of the thalidomide experience, however, it is understandable that both physicians and their patients continue to express concern over the safety of pharmacological agents, including anti-emetics, administered during early pregnancy. Caution is reasonable and it is accepted that medications be used during pregnancy only when absolutely necessary. While there are a number of options available to physicians, at this point in time, Dilectin (doxylamine succinate + vitamin B6) is the only medication approved by Health Canada for use as an anti-emetic in the treatment of NVP.[56]

For women who experience HG, timely treatment must address hypovolemia, electrolyte imbalances and ketosis. Results of one study, which indicated that, relative to controls, the mean dietary intake of most nutrients for women with HG was less than 50% of the recommended daily allowance,[57] highlights the fact that these patients are at high nutritional risk. Nothing should be given by mouth until dehydration is corrected and vomiting is controlled.[58,59] If the episode is prolonged, consideration should be given to vitamin supplementation, via the parenteral route.[60,61,62] Emotional support, perhaps including psychological therapy, is especially important throughout this time.[63,64]

PREVENTION

From all perspectives, prevention is always better than cure. In the case of NVP and HG, however, the absence of a causal model translates into tremendous difficulty in reducing the incidence of these conditions. Nevertheless, results of a randomized, double-blind controlled trial of periconceptual vitamin and mineral supplementation, initiated to demonstrate the effect of these supplements on the incidence of neural tube defects, indicated that these supplements also reduced the incidence of NVP and HG.[65] Although this appears to be "good news," this hypothesis remains to be proven in prospective randomized trials initiated specifically to examine this particular research question.

CONCLUSIONS

A wide variety of disorders have been implicated in the aetiology of NVP and HG. Future research must address the likely interplay of biological, psychological and social factors in the aetiologies of NVP and HG and utilize prospective methods in representative, sufficiently-large samples which would permit detailed examination of a number of factors in multivariable models.

Until the scientific community can elucidate the causal mechanism(s) underlying NVP and HG, clinicians must ensure that patients are provided with prompt and appropriate treatment(s), thereby ensuring optimal outcomes for mother and child.

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THE LONG TERM CONSEQUENCES OF POLYCYSTIC OVARY SYNDROME

By Tisha Joy, MEDS 2001

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, is the most common endocrine disorder in women of reproductive age.[1] In fact, it is the leading cause of pathologic amenorrhea in premenopausal women and is one of the leading causes of female infertility.[2] Approximately 75% of women with PCOS have fertility problems.[3]

PCOS is a heterogeneous syndrome characterized by an increased LH:FSH ratio (>2.5), elevated androgens, and anovulation.[4,5] Normally, LH stimulates ovarian theca cells to produce androgens such as 17-hydroxyprogesterone, androstenedione, and testosterone from cholesterol via cytochrome $P450_c$-17 alphahydroxylase. Ultimately, these androgens undergo aromatization by the FSH-stimulated granulosa aromatase.[6] However, in women with PCOS, the high LH levels cause ovarian theca cell hyperplasia, resulting in excess of these androgens and thereby halting follicular development within the ovary. Since a dominant follicle is not being formed, multiple cysts occur on the ovary, eventually causing impaired estradiol production.[2] This abnormal secretion of estrogen results in chronic anovulation, which may be manifest as amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding. In addition to these symptoms, acne, hirsutism, and/or male-pattern baldness may be present due to androgen excess.[7]

Androgen excess in PCOS may also occur due to the adrenal glands, resulting in increased levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), the latter hormone being a substrate for ovarian testosterone synthesis.[6] Although the exact role that adrenal androgens play in PCOS and the mechanisms involved have not yet been fully established, investigating the source of androgen excess in any individual patient is important in managing the symptoms of the androgen excess.

The prevalence of PCOS in the general population has been estimated to be about 5-10%.[8] It is interesting to note, however, that a recent study of healthy women found that 22% of these women had ultrasonic evidence of polycystic ovaries and 94% of these "normal" women with polycystic ovaries had at least one other symptom indicative of PCOS.[7] Yet, the importance of PCOS lies not in simply diagnosing cystic ovaries but in also understanding the associated long term consequences, including infertility, insulin resistance, non-insulin dependent diabetes mellitus (NIDDM), cardiovascular disease, and endometrial cancer.

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INFERTILITY

PCOS is often undetected until a woman experiences difficulty in conceiving.[3] The improper secretion of estrogen associated with PCOS causes cessation of follicular development and thus, lack of ovum release. PCOS is also a risk factor for repeated early spontaneous abortion related to the high LH levels and obesity.[9] About 50% of women with PCOS are obese.[4] In fact, obesity and hyperandrogenism contribute significantly to infertility via increased peripheral conversion of androgens (primarily, androstenedione and testosterone) to estrone within adipose tissue, thereby adding to the already abnormal estrogen secretion and menstrual disturbances present in PCOS patients.[10] Fortunately, diet modification and weight loss have been shown to improve these two contributing factors and thereby improve cycle regularity, ovulation, and fertility rates.[11,12]

INSULIN RESISTANCE AND NIDDM

Women with PCOS have a greater likelihood of having hyperinsulinemia and insulin resistance.[7] The exact mechanism responsible for insulin resistance is still under investigation. However, recent studies have shown that peripheral insulin resistance in adipocytes from PCOS patients may be due to decreased expression of the insulin-mediated glucose transporter protein GLUT-4.[13,14] Although insulin resistance would be expected to be more prevalent in obese women with PCOS, it was actually found to be independent of obesity.[14] Interestingly, patients with PCOS have double the risk of having subclinical bulimia and it has been postulated that this may also play a role in the insulin resistance in PCOS patients.[5,15]

Insulin resistance, common to most women with PCOS, is important in the development of NIDDM, the prevalence of which is seven times higher in PCOS patients than in the control population.[16] Moreover, NIDDM develops at an earlier age in women with PCOS (third to fourth decades) than in the general population (sixth to seventh decades).[1] Hyperinsulinemia is also a contributor to infertility since suppression of insulin concentrations by the use of metformin has been shown to improve fertility rate.[12] As well, it is an independent risk factor for cardiovascular disease due to its pro-atherogenic effects, including promotion of lipid plaque formation, smooth muscle proliferation, and growth factor production.[6] A recent study has shown that weight control and dietary intervention can increase insulin sensitivity (up to 93%) in obese women with PCOS and thus potentially decrease the risk of NIDDM or cardiovascular disease.[17]

CARDIOVASCULAR DISEASE

A number of risk factors for cardiovascular disease are present in women with PCOS. PCOS patients tend to have higher mean serum triglyceride levels as well as lower HDL levels compared to controls.[18,19] As discussed earlier, women with PCOS are prone to developing insulin resistance, hyperinsulinemia, and/or NIDDM, all of which increase the risk for cardiovascular disease. Based on the low HDL levels in women with PCOS and the correlation between low HDL levels and cardiovascular risk in the Framingham study, one author has estimated that women with PCOS have a relative risk of about 3 for cardiovascular disease compared with the general population.[20] However, since these risk factors of increased triglyceride levels, low HDL levels, obesity, hyperinsulinemia, insulin resistance, and NIDDM tend to cluster in women with PCOS, it would be reasonable to predict that the actual cardiovascular risk may be much higher, although no prospective study has yet quantified this risk.

ENDOMETRIAL CANCER

The risk of endometrial cancer is also increased in women with PCOS due to several factors: 1) lack of progesterone, 2) obesity, 3) hyperandrogenism, and 4). hyperinsulinemia. The lack of cyclical progesterone secretion results in unopposed estrogen effects, including endometrial hyperplasia. These effects may indeed be worsened in obese women with PCOS due to conversion of androgens to estrone within adipose tissue.[7] It has been found that obese women with an upper body fat distribution have a 5.8-fold higher risk of endometrial cancer than non-obese women or women with a lower body fat distribution.[21] Thus, both obesity and the distribution of body fat are important in assessing the risk of endometrial cancer for women with PCOS.

Hyperandrogenism may further contribute to the unopposed estrogen effect by providing additional substrate for conversion to estrone.[22] The relation between hyperinsulinemia and increased risk of endometrial cancer may occur through production of excess androgens. Increased levels of insulin cause decreased sex hormone binding globulin (SHBG) production, resulting in higher circulating levels of androgens.[10,23] High levels of insulin also cause a decrease in circulating levels of insulin growth factor binding protein 1 (IGFBP-1), thereby raising the levels of IGF-1. In response to LH, IGF-1 stimulates the ovary, resulting in increased activity of cytochrome $P450_c$-17 alphahydroxylase, the enzyme responsible for production of androgens. Thus, with the decreased SHBG levels and increased IGF-1 levels, ultimately increased estrone production occurs, thereby compounding the unopposed estrogen effect on the endometrium and promoting the risk of endometrial cancer.[24]

SUMMARY

PCOS is a relatively common female endocrine disorder that should be considered in all women presenting with menstrual disturbances, infertility, and/or hirsutism. It is associated with an increased cardiovascular risk due to obesity, insulin resistance or diabetes, high triglyceride levels, and low HDL levels. Further, unopposed estrogen contributes to the menstrual disturbances, anovulation, and infertility as well as to the increased risk of endometrial cancer in these women. Thus, the treatment and management of women with PCOS focuses on preventing the long-term consequences of PCOS by reducing obesity, decreasing androgen action, normalizing the endometrium, and correcting anovulation.

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UNDERSTANDING PREMATURE OVARIAN FAILURE

By Gina Rohekar, MEDS 2001

Premature ovarian failure (POF) is a condition that is characterized by elevated gonadotropins, hypoestrogenism and amenorrhea occurring in a woman who is younger than 40 years of age.[1] POF is not a rare condition; indeed, the incidence of POF before the age of 40 is estimated to be 1 in 100.[1] Despite the relative frequency of POF, there has yet to be found a definitive cause for its occurrence. Many theories have been proposed and researched as potential mechanisms for POF, and in some cases, specific causes have been found. However, for the most part, the etiology of POF remains obscure. The following article is intended as a summary of current theories used to describe POF.

WHAT IS POF?

In the early research into causes of POF, it was believed that the condition is a true "failure" of the ovaries in the sense that it is irreversible.[1] However, it later became evident that this is not the case. Follicle function appears to be at least intermittently maintained in most POF patients.[1] Studies have shown that follicles are present on pelvic ultrasound; as well, some POF patients have even become pregnant.[1] Thus, POF is not a complete termination of ovarian function. Rather, it is a condition of termination of normal ovarian function.

Clinically, a set of guidelines help to identify a patient as having POF. The patient must present with amenorrhea before age 40.[2] Laboratory criteria specify that amenorrhea should be present for more than or equal to 4 months, and that 2 serum FSH values of more than 40 mIU/mL are obtained at least 1 month apart from the patient.[2] Of particular note is that the progesterone withdrawal bleed test is not diagnostic in POF. This is due to the fact that some patients with POF may still intermittently produce enough estrogen for a withdrawal bleed to take place.[1]

CAUSES OF POF

A convenient way to examine potential causes of POF is by dividing the condition into two categories: i. patients with follicle depletion, thus resulting in POF; ii. patients with follicle dysfunction, thus resulting in POF.

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I. Follicle Depletion

If the normal contingent of follicles attributed to an ovary were somehow abnormally rapidly depleted, a patient may present clinically with amenorrhea and POF.[1] Some potential causes of follicle depletion include:

- abnormally low initial follicle endowment (as in cases of Turner's Syndrome or gonadal dysgenesis)[1]
- accelerated follicle atresia (determined in some cases to be due to balanced translocations of the X chromosome; two genes, POF1 and POF2 have been proposed)[1, 3]
- enzyme deficiencies such as galactosemia (deficiency in galactose-1-phosphate uridyl-transferase) which lead to accelerated follicle atresia, as above[1]
- chemotherapy, irradiation, or exposure to environmental toxins[1]

II. Ovarian Follicle Dysfunction

The category of 'ovarian follicle dysfunction' includes those patients with adequate gonadotropins, and follicles and oocytes that appear histologically normal yet they fail to have normal ovarian function.[1] This group consists of many cases of unknown etiology. However, some patient groups have been studied, leading to the discovery of a growing number of specific causes of POF in patients. These include:

- enzyme deficiencies, as related to defects in the 17α-hydroxylase enzyme, cholesterol desmolase, 17-20 desmolase and aromatase enzymes[1]
- signalling defects (defects in gonadotropins or gonadotropin receptors)[1]
- immune-related dysfunction (association with autoimmune diseases, antiovarian antibodies, steroid cell antibodies, zona pellucida antibodies or oophoritis)[1]

MANAGEMENT OF KARYOTYPICALLY NORMAL PATIENTS WITH POF

For patients that present with POF and who are karyotypically normal, there are a number of things that the managing physician can do to help the patient understand and cope with her condition. A general plan is to: i) Inform; ii) Counsel; iii) Replace; and iv) Follow-up.[1]

i. Inform

When diagnosed with POF, the patient should be provided with accurate and up-to-date information. The patient should be told that spontaneous remission of POF can occur, but that there is currently no known treatment for POF.[1]

ii. Counsel

The patient who is concerned about having children should be first advised to wait for the possibility of spontaneous remission. Adoption or a change in life plans should be offered as an alternative to couples. As well, a couple may be counselled to consider ovum donation after an appropriate waiting period.[1]

iii. Replace

In all cases of POF, there are definite indications for hormone replacement therapy to be implemented.[1] Full hormone replacement will not only reduce the patient's risks for osteoporosis and heart disease, but will also alleviate symptoms (such as vasomotor symptoms, vaginitis, dyspareunia and urinary frequency).[1]

iv. Follow-up

There has been some evidence correlating POF to autoimmune disorders and adrenal insufficiency.[1] Therefore, it is necessary to maintain a careful follow-up schedule with patients with POF.[1]

THE FUTURE OF POF

As molecular techniques are continuing to evolve, new avenues into POF research are appearing on the scientific horizon. Immunotherapies have been proposed, as well as studies into the role of apoptosis (programmed cell death) in POF.[1] Furthermore, new developments in the field of assisted reproductive technologies may increase options for couples with POF.[1] Current research at the University of Western Ontario is exploring the role of intercellular communication through gap junctions in the growing follicles in cases of follicular dysfunction (Dr. G.M. Kidder, Departments of Physiology and Obstetrics and Gynaecology). Interestingly, knockout mice models have been developed that are deficient in certain gap junctions expressed in the follicle or oocyte—resulting in female mice that are infertile, and express ovarian histology similar to that of women with POF.[4, personal communications from C. Ackert and G.M. Kidder]

Premature ovarian failure is a fairly common condition that patients may present with both to the family physician and to the gynaecologist. Study into causes of POF are continuously bringing to light new data and theories. Hopefully, this brief review will help put forth to medical professionals some of the current theories of POF and information to pass on to patients.

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ASPECTS OF FEMALE INFERTILITY

By Andrea A. White, MEDS 1999

INTRODUCTION

Infertility is a devastating problem for many couples. It is defined as a couple's unsuccessful attempt at conception after one year of unprotected intercourse. Primary infertility is a diagnosis that describes an infertile couple that has not previously achieved pregnancy, while secondary infertility denotes a couple that has achieved pregnancy prior to the onset of infertility.

Most industrialized countries report the combined incidence of primary and secondary infertility to be 10-15% of couples in their reproductive years.[1] Many couples are delaying conception, which results in increased risk of age-related infertility factors. There is also a rising incidence of sexually transmitted disease, which can result in tubal dysfunction. For these reasons, there appears to be an increasing trend of infertility. However, advancing technology, both diagnostic and therapeutic, as well as decreasing access and availability of alternatives, such as adoption, may prove this apparent rising trend to be factitious, or at least exaggerated.

There are numerous factors that may contribute to the etiology and pathogenesis of infertility in either or both of the partners. Initial evaluation by the Family Physician with appropriate and timely referral to a specialist may help the couple feel more comfortable with the process and prepare them for the possibility of further investigation or assisted reproductive technology.[2] The investigation, diagnosis and management of infertility can be difficult and frustrating for both the couple and the physician.

PHYSIOLOGY OF CONCEPTION

Numerous factors contribute to successful achievement and maintenance of pregnancy. Considerations for conception include both male and female issues, such as anatomy, endocrinology and metabolism, genetics, immunology, psychology and behaviour. Based on the collective effect of these factors, the statistical probability of conception in a given month is estimated at 20-25% in the normal population of child-bearing age.[3]

Male contributions to effective conception include the capability of vaginal intercourse and ejaculation of an adequate number of motile sperm. Therefore, requirements are normal spermatogenesis, semen production, as well as functional erection and ejaculation.[4]

In order to conceive, females must achieve normal folliculogenesis for development of a mature oocyte, ovulation and production of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol and progesterone in adequate quantity. These hormones regulate oocyte maturation, ovulation, proliferation and preparation of the endometrium for pregnancy, as well as amount and quality of cervical mucus. Therefore, female requirements for conception are proper hormone production and response, patent and functional fallopian tubes, appropriate uterine anatomy and effective oocyte-sperm interactions.[4]

Consequently, infertility may be the result of an isolated problem with any one physiological or anatomical element, or a combination of factors, and may involve either partner of the couple or both.

ETIOLOGY OF FEMALE INFERTILITY

Based on the assessment of contributory factors to successful conception, it is apparent that there are diverse causes of infertility. Common causes of female infertility are summarized in table 1. Several important topics have been selected for elaboration:

Table 1 - Etiology of Female Infertility [1]

Mechanism	Condition
Absent gonadal tissue	Turner's syndrome Pure gonadal dysgenesis
Impaired gamete production and function	Hypogonadotrophic hypogonadism Hypothalamic anovulation Hyperprolactinemic anovulation Androgen insensitivity Polycystic ovarian syndrome Premature ovarian failure Resistent ovarian syndrome Ovum retention Oocyte factor' (aged oocyte) Cytotoxic drugs Other drugs Irradiation ?smoking
Impaired gamete transport	Malfunction of ovum capture and cilia mediated transport Tubal infertility Endometriosis Cervical factor Antisperm antibodies
Impaired conception	Polycystic ovaries Smoking Abnormal sperm adhesion molecules
Recurrent miscarriage	Chromosomal aberrations Oocyte factor' (aged oocyte) Coagulation disturbances Polycystic ovaries Gross uterine anomalies

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Disorders of Ovulation

Dysfunction of ovulation is involved in 15 to 30% of cases of couple infertility.[4] Hypothalamic disorders result in anovulation and amenorrhea due to an abnormality of pulsatile secretion of GnRH, which impacts upon normal LH and FSH secretion. Approximately 20% of women with amenorrhea are found to have a pituitary abnormality, such as a prolactinoma.[4] Other endocrine disorders which can potentially lead to infertility are thyroid dysfunction and adrenal gland disorders, including congenital adrenal hyperplasia, adrenal tumour, Cushing's disease and Addison's disease.

Ovarian dysfunction may result in anovulation. Polycystic ovary syndrome is commonly associated with infertility. Aside from the anovulatory disturbances, this condition is associated with hirsutism, obesity, dysfunctional uterine bleeding and endometrial carcinoma. Investigations reveal elevated LH, normal or low FSH and slightly elevated testosterone levels. Ovaries contain multiple follicles arrested at 0.5 to 1.0 cm diameter. Resistant ovary syndrome, which results from decreased sensitivity to FSH leading to failure of maturation of primordial follicles, primary ovarian failure and other ovulatory disorders are potential factors in infertility. The 'oocyte factor'[1] or 'reluctant ovum syndrome'[4] refers to the aging oocyte's reduced capacity to be fertilized and undergo normal division. Lower pregnancy rate, higher abortion rate and rising incidence of fetal chromosomal abnormality is associated with increasing maternal age.[1,4]

Disorders of Transport

Impaired function or blockage of the fallopian tubes have strong associations with pelvic inflammatory disease (PID), tubal ligation, pelvic surgery, previous ectopic pregnancy and endometriosis. Tubal factors are relevant in 12-20% of infertility cases.[4] PID is caused by an infection of the upper genital tract. Specific sexually transmitted infections, such as Chlamydia trachomatis or Neisseria gonorrhoeae are implicated in 60-80% of cases.[5] The symptoms include pelvic pain, vaginal discharge, fever, vomiting and abnormal bleeding. Signs include cervical motion and adnexal tenderness, palpable mass, fever, and cervical discharge. Pathology frequently shows cervicitis, endometritis, pelvic peritonitis, and, most relevant to fertility, salpingitis. For each episode of infection, there is a 10% or greater risk of tubal infertility and each subsequent infection represents a cumulative risk. For example, the risk of infertility is 35% with a second infection and 75% with three or more episodes.[5] Damage related to PID accounts for between 20 and 56% of ectopic pregnancies, which can be a compounding risk factor for infertility.[6]

Endometriosis is a common cause of infertility. Although controversial, estimates of the incidence of endometriosis among females of infertile couples range from 20 to 50% and there is clearly a reduced rate of conception among these women.[7] Even mild endometriosis may result in reduced fertility by leading to pelvic adhesions, ovarian or tubal damage. Mechanisms proposed for infertility include direct obstruction of the tubes, prostaglandin-induced tubal dysfunction resulting in decreased transport capacity, ovulatory dysfunction and luteinized unruptured follicle syndrome, as well as cell-mediated immune system alterations and increased leucocytes in the peritoneal fluid that may alter conception and implantation.[7]

Cervical mucus of inadequate quality and quantity or containing antisperm antibodies may interfere with mucus-sperm interactions and transport, although this remains controversial as an isolated factor in infertility.[8]

Disorders of Implantation

Uterine pathology is a rare cause of infertility.[9] Uterine abnormalities, such as bicornuate uterus or uterus subseptus, Asherman's syndrome, intrauterine adhesions endometrial ossification, leiomyoma and adenomyosis constitute some of these etiologies. Hormonal disorders causing decreased endometrial receptivity are other potential mechanisms resulting in infertility.

Chromosomal Abnormalities

Although not initially presenting with infertility, phenotypic females with chromosomal abnormalities such as gonadal dysgenesis, including Turner's syndrome, and androgen insensitivity, are sterile. Habitual abortion, recurrent loss of 3 or more pregnancies, is experienced by 0.5 % of the population. Investigations have shown that in 10-20% of these couples one partner will have a chromosomal abnormality, such as 47,XXX, 47,XXY or a balanced translocation.[10]

Of spontaneous abortions occurring in the first 8 weeks of gestation, 50% are due to chromosomal abnormalities of the fetus. Trisomy, polyploidy and 45,XO are common karyotypes that may result in lethal conditions.[10] Many women are not aware of the pregnancy, and this may be perceived as failure to conceive.

Behavioural and Psychological Factors

From a careful history, sexual behaviours and misconceptions can be ascertained. Education regarding normal pregnancy rates, timing of intercourse, adequate penetration and drug and alcohol use may be required. There is some evidence to suggest a delayed rate of pregnancy among women who smoke.[1] Effects of other lifestyle issues are less clear.

Psychological factors can have a great impact on infertility. Whether or not they actually cause infertility is controversial, but it is clear that they definitely contribute to it. Questions regarding impotence, premature ejaculation and decreased libido are important for the male partner. Female issues include stressful life events, anorexia nervosa, depression, anxiety, decreased libido and vaginismus.

Unexplained Infertility

Idiopathic infertility is a diagnosis of exclusion that applies to patients whose investigations have not revealed a known etiology. With advances in diagnostic

techniques, the incidence of infertility that remains unexplained after appropriate diagnostic investigations has been declining since the 1950's, when it was reported at greater than 20% of infertile couples.[11] Current estimations of idiopathic infertility range from 10 to 15%.[12,4] Possible etiologies include subtle sperm function defects, subclinical endocrine abnormalities, immunological factors and infection.[13] Without treatment, there is a reported pregnancy rate of 60% within 3 years, which evokes the theory that there may be no abnormality at all, or one that resolves spontaneously.[13]

Multifactorial Infertility

Approximately 20% of couples experiencing infertility are shown to exhibit a combination of factors relating to their difficulties.[14] Infertility may be attributed to more than one factor in one partner or a combination of factors in both partners. Although not addressed in detail throughout this discussion, male factors contributing to infertility may include disorders such as those listed in table 2.

DIAGNOSING FEMALE INFERTILITY

Evaluation of a couple's diagnosis of infertility includes an attempt to determine the probable cause, education, support, counselling for the couple and a review of the treatment options. Both partners should participate in all aspects of the evaluation and decisions regarding treatment. This allows assessment of the couple's relationship, level of understanding and ability to cope. It is also an important indicator of the couple's support and commitment to each other.

A thorough evaluation of the contributory factors to infertility will reveal a probable cause in 85-90% of couples.[14] The remaining 10-15% may have multiple combined causes or a more subtle cause of their infertility that leaves them with the frustrating diagnosis of unexplained infertility.

The History and Physical Examination

The history should focus on the factors required for successful conception. These factors include male and female determinants. Both partners should be assessed for factors involved in infertility. Onset, duration and primary versus secondary infertility should be determined from the history. The rest of the interview should be composed of a review of presenting and associated symptoms, previous obstetrical and gynecological history, including sexual history, menstrual history, attitudes towards sex, sexual practices (timing and frequency of intercourse, method of contraception), general medical and surgical history, medications and social history (smoking, nutrition, weight, exercise, drug and alcohol use).

A complete physical examination must be done, focusing on the signs and physical findings of the causes of infertility. For example, polycystic ovary syndrome is associated with hirsutism, acne, obesity, and acanthosis nigricans. During the pelvic exam, enlarged or nodular ovaries, uterine or adnexal masses or tenderness and fixation of pelvic structures may be demonstrated in relation to specific suspected diagnoses.

Table 2 - Etiology of Male Factor Infertility [14]

Mechanism	Condition
Endocrine disorder	Hypothalamic dysfunction (Kallmann's syndrome) Pituitary failure (tumor, radiation, surgery) Hyperprolactinemia Exogenous androgens Thyroid disorder Adrenal hyperplasia
Anatomic disorder	Congenital absence of vas deferens Obstruction of ejaculatory system
Spermatogenesis abnormalities	Chromosomal abnormalities Mumps orchitis Cryptorchidism Chemical or radiation exposure Varicocele
Motility abnormality	Absent cilia (Kartagener's syndrome) Varicocele Antibody formation
Sexual dysfunction	Retrograde ejaculation Impotence Decreased libido

Table 3 - Common Tests for the Evaluation of Female Infertility [4]

Test	Factor Evaluated
Pregnancy test	Pregnancy
CBC, Glucose	Underlying medical conditions
TSH	Thyroid disorders
Prolactin	Prolactinoma
Serum FSH, LH	Polycystic ovarian syndrome Premature ovarian failure
Testosterone	Polycystic ovarian syndrome Ovarian tumor
17-Alpha hydroxyprogesterone	Adrenal hyperplasia
Progesterone challenge	Endogenous estrogen endometrial proliferation
Post-coital test	Cervical mucus Sperm motility
Endometrial Biopsy	Secretory endometrium
Hysterosalpingography	Genital tract anatomy
Laparoscopy	Tubal patency and anatomy Endometriosis Adhesions
Hysteroscopy	Intrauterine abnormalities
Vaginal Ultrasound	Polycystic ovaries
Vaginal, cervical swabs	Infection

CBC=Complete Blood Count; FSH=Follicle Stimulating Hormone; LH=Leuteinizing Hormone

Investigation of Female Infertility

Aggressive evaluation is indicated in patients presenting with abnormal uterine bleeding, amenorrhea, endocrinological symptoms, longstanding infertility or maternal age over 35 years. Pregnancy should be ruled out in amenorrheic presentations. Often a suspected diagnosis will present with the initial history. The approach is determined by the wishes and availability of the couple, the cost of the tests and the potential treatment options. Table 3 summarizes the major tests for evaluation of infertility and the factors being evaluated.

IMPACT AND IMPLICATIONS OF INFERTILITY

Few couples consider infertility until their attempt at conception fails. In most cases, it is a diagnosis that is unanticipated and interrupts longterm planning. Many intense feelings may be associated with the realization that they may not conceive as planned. Feelings of guilt, grief, inadequacy and shame tend to dominate initially. Similar to individuals experiencing death of a loved-one, couples may cope with the diagnosis in progressive stages, including denial, bargaining, anger, grief and resolution. Anger can be accompanied by frustration, rage or jealousy and resentment of other couples' successes.[14]

Dominant beliefs of society worldwide support the view of parenthood as imperative for "personal fulfillment, social acceptance, achievement of full adult status, religious membership, sexual identity and psychologic adjustment".[15] There is a social stigma that is inflicted upon infertile couples for "failing to fulfill a cultural norm".[16] According to Miall,[17] North American society is procreative and upholds two fundamental philosophies: that married couples should have children, and that married couples should want to have children. Infertile couples can feel a sense of social isolation and a loss of identity.

Although some couples report difficulty in relationships with family and friends, Danulik's[15] studies suggest that investigation and treatment of infertility may actually increase the level of trust, intimacy and communication perceived by the couple in their relationship. Similarly, sexual satisfaction and functioning were reported by Danulik[15] not to have been negatively impacted by the diagnosis, or the investigations. Negative consequences of investigations, however, have been reported to be a loss of dignity and privacy.[16] Other issues raised were the impacts of the results of testing. For example, perhaps the most frustrating diagnosis is that of unexplained infertility. Not only do couples not have a disease process to blame, they do not have a specific treatment plan.

Most couples agree on the importance of feeling free to express their thoughts, fears, feelings and questions. Both partners should have access to counseling and support groups. Insight into feelings and behaviours can help prevent depression, while strengthening existing relationships. Many couples are comforted by hearing the feelings and experiences of others in similar situations and understanding that they are not alone. Counseling, support and education should be a primary goal of all infertility evaluations. There are various resources available for this purpose (Figure 1).

MANAGEMENT OF FEMALE INFERTILITY

Management of infertility includes medical or surgical therapy in conjunction with counseling and education. Choice of treatment options must be evaluated by the couple and the physician on the basis of the investigation results, diagnosis, time and effort commitment, treatment side effects, psychosocial issues, expense, and the couple's attitudes, experiences and wishes. Table 4 summarizes the recommended treatments for specific etiologies of

Figure 1 - Resources available for Support , Counseling and Patient Information

What resources are available

Support Groups	**1. Infertility Awareness Association of Canada (IAAC)**, Ottawa - Tel: 1-800-263-2929 or (613) 730-1322 **2. Infertility Self-Help Support Groups**, London - Tel: (519) 668-3895 or (519) 672-7605 **3. Infertility Network, Toronto** - Tel: (416) 691-3611 **4. Gamete Donation Advocacy and Support Group**, Toronto - Tel: (416) 762-0103 **5.Infertility/Adoption Helper**, Toronto - Tel: (416) 690-9593 Email: helper@helping.com
Web Site Information	http://www.cdnfertility.com/fertility
Reading Materials	**1. Surviving Infertility: A Compassionate Guide Through the Emotional Crisis of Infertility**, by Linda P. Salzer. New York: Harper Collins, 1991. **2. Making Babies - A Complete Guide to Fertility and Infertility**, by Heather Pullen and Jocelyn Smith. Toronto: Random House, 1990. **3. The Long-Awaited Stork: A Guide to Parenting After Infertility**, by Ellen Glazer. Lexington, Massachusetts: Lexington Books, 1990. **4. Without Child - Experiencing and Resolving Infertility**, by Ellen Glazer and Susan Cooper. Toronto: 1988. **5. Adopting After Infertility**, by Patricia Irwin Johnston. Indianapolis: Perspectives Press, 1992. **6. The Canadian Adoption Guide**, by Judith Wine. Toronto: McGraw-Hill Ryerson, 1995.

infertility and the respective success rates. In addition to these conventional therapies, advanced techniques, referred to as assisted reproductive techniques (ARTs), may be considered. These procedures may be indicated, as determined by specialists, in such conditions as fallopian tube damage, endometriosis, cervical factor infertility, unexplained infertility, male factor infertility and failed conventional therapies.[18]

In Vitro *Fertilization (IVF)*

The current preferred method of in vitro fertilization and embryo transfer (IVF-ET) requires controlled ovarian hyperstimulation in order to induce follicle maturation for maximum potential yield of oocytes. Oocytes are removed from the ovary, fertilized *in vitro*, and returned to the uterus. This technique first resulted in the successful birth of a child on July 25, 1978, to the credit of the British team Steptoe and Edwards.[19] Since then, the success rate has dramatically improved and has gained world-wide recognition in the management of human infertility. The pregnancy rate is approximately 20% per embryo transfer per IVF cycle.[20] To increase the potential for pregnancy, more than one embryo is transferred, and therefore, increases the risk of multiple gestations.

Problems with IVF-ET include financial expense, complications of multiple gestations or ectopic pregnancy,[21] as well as cancellation of cycles due to inadequate response to stimulation, premature LH surging and excessive hyperstimulation that promotes oocyte dysmaturity. Excessive stimulation has been associated with ovarian hyperstimulation syndrome, characterized by ascites, pleural effusions, hypercoagulability and pain secondary to ovarian enlargement.

Gamete Intra-Fallopian Tube Transfer (GIFT)

GIFT is a technology that uses the same techniques as IVF for hyperstimulation and harvest of oocytes. The oocytes are combined with capacitated sperm and replaced in the fallopian tubes for natural fertilization and development. Reported pregnancy rates of 20-30% per cycle tend to be slightly higher than those of IVF techniques, but normal tubal function is required.[20]

When to Refer to a Specialist

Consultation by a specialist requires referral by a family physician, gynecologist or urologist. Family physicians should instigate initial evaluations. Surgical treatment and medical therapy beyond administration of clomiphene, bromocriptine and progesterone require the expertise of a specialist. In addition, physicians not comfortable in the role of counselor and educator should refer their patients to a specialist, social worker, psychologist or other professional trained in this capacity. Recognition of when to refer is important in order to minimize anxiety, discomfort and expense, as well as to maximize potential success.

Table 4 - Conventional Treatments for Infertility [1] and their respective Success Rates [4]

Etiology of Infertility	Treatments	Success Rate
Ovulatory factors	Clomiphene Gonadotropins Pulsatile GnRH	50-90%
Hyperprolactinemia	Bromocriptine	N/A
Cervical factors	Estrogen supplementation Intrauterine insemination	N/A
Tubal damage	Tubal surgery	20-30%
Adhesions	Lysis of adhesions	50%
Endometriosis	Surgical ablation	35-60%
Unexplained	Clomiphene Gonadotropins Intrauterine insemination	3%

GnRH=Gonadotropin Releasing Hormone

The London Program for Treatment of Infertility

The Department of Gynaecology and Reproductive Medicine at University Hospital Campus of the London Health Sciences Centre offers numerous services and programs for the management of infertility. In 1972, the Therapeutic Donor Insemination program was developed and since then, boasts more than 1200 pregnancies. The IVF program was established in 1985 and proudly reports over 850 births. The year 1993 saw the first baby born following embryo cryopreservation. Subsequently, in 1994, the most recent addition to this internationally renown centre became the intracytoplasmic sperm injection (ICSI) program, for the treatment of male infertility.

CONCLUSION

The diagnosis of infertility is a devastating one. It targets young, otherwise healthy individuals and strikes without warning. It is important that couples have access to accurate, updated information and adequate supports in order to make informed decisions regarding their futures. Research continues to make advances in the areas of infertility diagnosis and treatment. These advances promise better safety and improved success rates.

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THE ROAD AHEAD: FEMALE PHYSICIANS AS ROLE MODELS

By Rachel Rodin, MEDS 2000 and Romy Saibil, MEDS 2000

In the first two years of the University of Western Ontario's medical undergraduate curriculum students are exposed to a variety of clinical disciplines and professional teaching styles, which influence their choice of electives and research projects during their early medical education. Later, during the clinical clerkship, students base their career decisions partially on the contact they have had with clinicians from the various specialties. Exposure to women physicians at both of these stages is minimal, and female role models within academic medicine (particularly at the senior level) are lacking. Consequently, most students' vision of their career forms without the inspiration and support of female leaders. The lack of female lecturers and clinical teachers reflects a marginal representation of women across the board in the Faculty of Medicine and Dentistry (Table 1).

As third year students we recently completed the in-class component of our training. We found exposure to women physicians to be minimal. The picture for the next two years of our education recapitulates that of the first two years: a dearth of female physicians as role models and mentors. While there is a high degree of female representation in the planning of the new curriculum, the outlook for first year students is not likely to vary from our experience. Course coordinators can only select lecturers from the fund of women academics that exists at Western—a fund which is limited and increasingly overburdened.[1,2]

The medical school at UWO has 17 women who are Full Professors. This follows the pattern of other major medical schools in North America, which have, on average, sixteen female full professors of clinical and basic sciences.[3] At Western this figure compares to 259 full professors who are men. At the senior academic level of UWO, there is an eight to one ratio of males to females; at the junior academic level, the ratio of men to women is three to one (See Table II). If the junior faculty progresses as expected along the academic path, the representation of women at the senior faculty level should eventually approach three:one as well. Unfortunately, research has shown that female physicians often fail to advance at the same rate as male physicians within academia. In a report by Dickstein, it took an average of 20 years for women to advance to the position of full professor while for men, it took only 12 years.[4] Similarly, a national U.S. study by Tesch demonstrated that, women are not as likely as men to attain the position of associate professor or full professor after approximately eleven years of faculty service.[5] Even after adjustments were made within the study to account for the fact that women reported less academic productivity with respect to hours worked, articles published, and grants received they were still substantially less likely to be promoted than men.[5] Relying on the slow movement of Western's junior academics up into the senior ranks may therefore not be the best solution to improving the representation of women on the Faculty. If junior women are not yet qualified for specific senior positions, which become available, an active effort should be made by recruiters to encourage applications from qualified women at other institutions. There is, however, a general consensus among members of the Gender Issues Committee and Dr. McMurtry, the Dean of Medicine and Dentistry, that this type of an affirmative action program at UWO would not benefit the status of women. If appointed in association with an affirmative action program, a woman may not be viewed as having earned a "right" to her position; in this way, her authority in the position may be undermined, as may be her ability to garner collegial support.[2,6]

Table 1-FEMALE vs. MALE REPRESENTATION IN MEDICINE AT UWO

Specialty	Male	Female	Specialty	Male	Female
a. Anaesthesia	53	15	k. Ophthalmology	18	0
b. Neurological Sciences	34	7	l. Otolaryngology	16	0
c. Radiology & Nuc. Med.	64	9	m. Paediatrics	50	27
d. Family Medicine	115	52	n. Pathology	24	12
e. Medicine	160	26	o. Psychiatry	108	32
f. Obstetrics & Gynecology	41	4	p. Surgery	77	5
g. Oncology	28	8	q. Physical Medicine	9	2
h. Anatomy & Cell Biology	19	3	r. Biochemistry	34	5
i. Epidemiology & Statistics	21	12	s. Micro. & Immuno.	37	5
j. Pharmacology & Tox.	19	2	t. Physiology	33	4

Table 2 - FEMALE vs. MALE REPRESENTATION AT THE SENIOR ACADEMIC LEVEL OF UWO

Position	Male	Female
Senior Faculty (Full and Associate Professors)	370	45
Junior Faculty (Assistant professors, Lecturers and Instructors)	281	97

ABOUT THE AUTHORS

Rachel Rodin and Romy Saibil are both third-year medical students at the University of Western Ontario. Rachel Rodin completed a BSc in Northern Studies from McGill University and maintains an interest in Native Canadians and social justice. Romy Saibil obtained a BSc in the Scholar's Elective Program with a concentration in Statistics at the University of Western Ontario.

A number of reasons have been presented to explain the under-representation of women in academic medicine. First and foremost is the issue of choice. Many women do not choose a career in academic medicine because of the demands on their time and quality of life. It is important to note that women physicians' choices are made from a limited set of opportunities.[7]

To root the rationale for Western's statistics solely in women's individual choices, attitudes, and productivity would be implying that education, recruitment and promotion systems are always fair and based on merit alone. As has been suggested by Dr. Nicole LeRiche, Director of Admissions, and Chair of the Medicine Admissions Committee, oftentimes a faculty selection committee identifies "merit" based on an outdated model crafted by men. Further, it is by and large men who sit on the selection committees at Western. For example, there are currently two active selection committees. The Oncology committee consists of nine men and two women and the Physical Medicine and Rehabilitation committee is composed of twelve men and no women.

In addition to accepting the need for a new definition of merit, we would do well to recognize that medicine is not a meritocracy and never has been. Choices for promotion and hiring are based on personality, gender, values, age, and sociocultural similarity to the inner circle of the specialty, the so-called "locker-room advantage." Similarity of a candidate's traits to those of the dominant group are perceived to create the most trustworthy colleague.[7]

Since early in his term Dean McMurtry has strongly advocated recruiting and promoting female staff. He has also supported the activities of the Gender Issues Committee (GIC). The GIC is a committee primarily concerned with policy and education issues related to gender. A budget exists for promoting and helping with activities of the GIC, but it has not been fully utilized in the past.[6] Other initiatives from the Dean's office have included: the encouragement of physicians with sick children to remain at home with them; the abolishment of meetings held outside of work hours; and the recent establishment of job sharing. Once the opportunity to job share becomes widely known it will allow for careers in highly demanding specialties to become more feasible for women.

Belle Potts, the resource person for the GIC and Counselor/Coordinator for the office of Student and Equity Affairs, recounted two ways in which the GIC has been active in the Faculty selection process. First, the GIC developed a list of questions designed to assess all candidates' sensitivity to gender issues. These questions were given to the selection committee members who were to interview candidates. Second, Dean McMurtry requested that a member of the GIC sit on every selection committee.[1] This GIC representation has proven difficult due to the fact that the number of selection committees frequently exceeds the number of GIC members. In addition, members of the GIC are stressed by other clinical and academic responsibilities. At some Canadian medical schools, such as the University of Ottawa, there is a faculty member who is appointed as Dean of Equity. Western's Faculty would also benefit from the appointment of a person whose unique mandate is gender issues.

Working with selection committees to improve the hiring and promotions process is only one way of opening more doors to women in medicine. At the same time, the Faculty of Medicine and Dentistry should actively encourage contact between female faculty and medical students as it is vital to the way in which young women perceive their roles in medicine. Better contact can be achieved through increased involvement of women in clinical teaching and through mentoring. Little research has been done on the possible impact of increasing the exposure of women students to women consultants in the early years of medical training. On the other hand, mentoring has been a topic of discussion in the literature and there is evidence for its efficacy.

Mentors are those individuals who have been ahead of us on a given career, social or personal path. Consequently, they are able to act as guides on that path; they encourage, point out obstacles, reveal secret short cuts, and introduce one to fellow travelers. Overall, mentors can smooth the way for a newcomer and build a sense of belonging. In particular, mentors may be helpful to women because studies have illustrated that men and women approach career development differently. Lorber suggests that "Men are likely to have a sponsor during training and to fall into serendipitous training opportunities. Women tend to pattern themselves after role models, who give only indirect guidance, rather than active help."[7]

Finding female mentors at Western may be a difficult for some students, due to the lack of exposure to female consultants on the lecture circuit and due to the limited numbers of women in leadership and chair positions. Historically, mentor-student relationships have been underutilized by women often owing to the complications of mixed-sex mentoring.[8] In spite of the difficulties with mixed-sex mentoring, it is important that it continues.

Mentor groups have been set up at the University of Western Ontario wherein a faculty member is grouped with several students from each year of medical school. Together they form a "mentor group". The mentor group does not always, however, provide one to one contact with a physician in a student's discipline of interest. An informal mentor group has also been set up among female consultants and residents in Paediatrics. The Organization for Medical Gender Awareness (OMEGA) was created in 1995 and has now been changed to the Medical Education for Societal Awareness group (OMESA); this group of undergraduate medical students also sets up programs which bring female physicians into contact with female medical students. All of these programs are set up to facilitate mentoring.

Without a past degree, or personal connections, students have their lectures, small groups, and career nights on which to base their early decisions regarding with whom to spend valuable elective and research hours. The question arises as to whether female students will view certain fields, and academic medicine itself, as a realistic choice when so few women are present in the classroom as well as the hospital teaching environment. For instance, there were no female lecturers in the entire second year Surgery block. It is difficult to imagine that

this absence of female physicians would not have impact on students, particularly female students in search of role models.

Under-representation of female faculty at the lecturing and clinical teaching levels, creates a paucity of women role models for both female and male students. Although the goal of this article has not been to evaluate career choices and placement for residency training, our contention is that a lack of female role models may be discouraging to undergraduate female medical students. Women's concept of their role in medicine crystallizes in a relative vacuum of female leadership. It would be naïve to suggest that networking exists less in the medical profession than anywhere else. Thus, if advantages accrue in medicine they begin at the undergraduate level and blossom exponentially. This complex process of accumulated advantages and disadvantages underscores the importance of exposing medical school classes to both male and female professors.

ACKNOWLEDGEMENTS:

We would like to thank Belle Potts, Admissions/ Student and Equity Affairs, for her advice and for providing research material pertaining to this article. Many thanks to Dr. Nicole LeRiche, Director of Admissions and Chair, Medicine Admissions Committee, and Dr. McMurtry, Dean of Medicine and Dentistry for their willingness to share their views.

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EMPOWERMENT OF KNOWLEDGE: Sharing Information with Young Girls and Medical Students about Menstruation

By Jessica Baugniet, Lisa Calder, Kim Moore, Kathleen van Hooren, Susan Woolhouse, Melissa Yuan-Innes, MEDS 2000

This project on menstrual education has distant beginnings in the personal experiences of two of the authors. In their high school years, they formed a group with other young women to share their menstrual experiences and attempt to remove the secrecy that enshrouds the subject. A consensus was reached that many women and men seemed to have a very negative perception of menstruation in general. Four years later, the two authors introduced these ideas to a group of women in their first year medicine class at UWO. The group's enthusiasm for these ideas developed into an opportunity to do an honours PBL project, entitled "Sharing Information with Young Girls about Menstruation".

The overall aim of our project was to communicate the experience, as well as the sociocultural and biological meanings of menstruation through the use of an integrated approach that embodied personal and collective experiences, comfort with self, empowerment and autonomy[1]. We addressed this objective in three ways: evaluation of current menstrual education and local resources for young girls; creation of a workshop for young girls about menstruation; and creation of a workshop for medical students about menstruation.

THE EVALUATION PHASE

We devoted the first year of our project to the evaluation of current menstrual education and resources for young girls. To accomplish this, we took a variety of approaches, beginning with a survey of the resources available at the London Public Library and a review of the London Board of Education elementary school curriculum. We followed this with interviews with local schoolteachers regarding their views on menstrual education. We investigated available resources and programs offered through the London-Middlesex Health Unit in addition to interviewing local family physicians and a child psychiatrist regarding their approach to the topic of menstruation with young girls in their medical practices. Finally, we consulted the academic literature about the psychological framework of menstruation, the social context, and the cultural issues surrounding menstruation.

ABOUT THE AUTHORS

The authors are in the class of Meds 2000 and wrote this article as they concluded a two year honours PBL project. They look forward to extending the project with the help of Meds 2001.

By examining available public resources as well as the current public school curriculum and its implementation, we were able to obtain a comprehensive picture of menstrual education of young girls in London. While teachers and public health nurses work hard at enacting the curriculum, there remain the powerful influences of media and the subtle effects of culture which engender a negative attitude towards the menstrual experience. Thus, we concluded there was room for a positive, woman-friendly approach to teaching menstruation beyond the traditional biological perspective. The reviewed research supported that young girls need positive, practical information on menstruation and, in fact, it has been shown that increased knowledge is correlated with a positive menarcheal experience[2]. Physicians and teachers alike were supportive of this approach and recognized the need. Our report also indicated that future physicians are not made aware of menstrual issues beyond biology through the UWO Faculty of Medicine curriculum. We concluded that heightening the sensitivity and awareness in these areas was in the best interest of all members of any health partnership. Based on the findings, we proposed innovative workshops for both young girls and medical students.

THE MENSTRUAL WORKSHOP FOR YOUNG GIRLS

In the second year of the project, we divided into two groups to tackle the further development and implementation of each workshop. The purpose of the interactive educational session for young girls was to communicate the integrated experience, sociocultural meaning, and biological meaning of menstruation in a positive, woman-friendly manner. Acting upon the suggestion of a community member, we contacted the Children's Aid Society (CAS) as a potential pilot group for the workshop. Laverne Foran, social worker at the CAS, recommended the "Pre-Teen Group", a counseling group for 11-13 year old girls who have been the victims of sexual abuse. While we were initially hesitant to undertake the workshop with a group of girls having a complex array of additional issues, after several discussions and the encouragement from the CAS, we decided to pursue the proposal. With the support of CAS, we intentionally did not alter the workshop to address the issues of sexual abuse; rather, we created a picture of menstruation as a normal, healthy process in every young woman's life.

We conducted the workshop over two evenings with seven girls from the previously mentioned Pre-Teen Group and the CAS Pre-Teen Group coordinators. On the

first evening, we asked each girl to create and present to the group a paper collage from provided magazine materials depicting what menstruation meant to her. It was an excellent activity to promote discussion of a commonly silenced topic. This led into an interactive discussion in which the girls identified the changes of puberty and subsequently added these changes to a feltboard model of a pre-teen girl. Through the discussion of secondary sex characteristic development and the biology of menstruation, this activity demonstrated several misconceptions held by the girls in the group. In fact, extra time was required to complete this activity in order to provide the girls with correct information regarding the process of puberty and menstruation. With the knowledge base reinforced, we then discussed the practical issues of the experience of menstruation such as how a girl's period looks, feels, and smells.

On the second evening, we addressed many questions from the previous session. Then we circulated a series of menstrual supplies including pads and tampons for the girls to examine. A step-by-step interactive demonstration was used for both pad and tampon use. This was followed by the viewing of a video in which the presenters were shown entering a drugstore and purchasing menstrual products. While the opportunity to ask anonymous questions had been provided, the girls felt comfortable enough to ask them outright. The session was concluded by handing out a pamphlet that contained some frequently asked questions about menstruation (Table 1).

After the workshop was completed, the presenters met with the CAS social workers for feedback. It was noted that initially many girls seemed reluctant to discuss menstruation in a group setting but that their comfort level visibly changed after they put together their collages. The openness and level of honesty of the presentation seemed respected by the girls in the group and enhanced the educational experience. In particular, the fact that misconceptions about the physiology of menstruation were revealed and dealt with was very helpful. The social workers felt that having the pads and tampons available for the girls to look at and touch helped prepare them for their menstrual experiences. Another interesting finding in the workshop was that many girls were unaware that they could speak to their physicians about menstruation and the encouragement of this dialogue seemed effective. The girls write in journals after every session and the social workers indicated that the entries reflected a valuable workshop. The social workers were pleased with the success of the workshop and expressed interest in incorporating this kind of workshop into their regular program. We are currently working with members of Meds 2001 to bring this about for the 1999 spring session.

THE MENSTRUAL WORKSHOP FOR MEDICAL STUDENTS

We decided to create a workshop for medical students because we believed it was important to address the physician's role in educating young girls about menstruation. When reviewing the literature, we discovered several articles discussing the benefits of menstrual education in terms of the impact on a young

Table 1 - MENSTRUATION PAMPHLET FOR YOUNG GIRLS

Beginning to menstruate, or having your first period, is a natural event which women experience. It may seem scary, as it involves changes in your body, but knowing the facts can help you feel in control during this time of change.

When will I get my period?

Young women start menstruating at different ages, although many young women have their first period between the ages of eleven and fourteen. It's normal that some will have their first periods earlier or later. If you are concerned about your timing, you can ask your doctor.

What do periods feel like?

While some women are unaware that they are having their periods, others may feel a bit of blood leaving their vaginas. Women may feel cramps in their lower stomachs. These cramps can often be relieved by exercising, having a hot bath, or using a hot water bottle.

How much blood is lost?

Not as much as it may look or feel like! Most women lose about a half a cup of blood.

What happens if you get your period at school?

It's a good idea to keep a pad or tampon in your desk and bag in case of an emergency. Your teacher or the office will have supplies, if you have run out or don't have money to buy them. It's perfectly normal to have very unpredictable periods early on - so be prepared!!

Does it mean I am dirty when I menstruate?

Absolutely not!! Menstruation is a not a dirty process. As long as you keep up with your normal daily hygiene (showering, changing pads every 4-6 hours etc.) there should be no strong odour. A little odour, however, is normal. You don't need to use deodorant pads or tampons because they can cause rashes.

Who can use tampons? Are they safe?

All girls can use tampons, but many wait until they are a bit older because using them takes practice. Remember, tampons cannot get lost or pushed up too far. It is important to change a tampon every 4-6 hours because there is a rare disease called Toxic Shock Syndrome that is associated with leaving tampons in too long. Tampons are useful because you can wear swimsuits and swim while using one. You do not need to be sexually active to use a tampon.

What is P.M.S.?

P.M.S. or "Premenstrual Syndrome" is a mood change experienced by some young women just before they get their period. Some women feel happy, hungry, a bit sad, or just different. After time, you will start to figure out what is normal for you, and you can let that feeling be okay.

If I have been abused, will that affect my periods?

Abuse can be a very complicated issue – we encourage you to speak to your doctor if you are or have been abused. They will have information and resources available to help you.

girl's menstrual experiences. Studies[2] have shown that an increase in knowledge about menstruation will decrease the stress and trauma at menarche, a developmental milestone in the lives of young girls. Several surveys[3] have demonstrated that girls and boys can develop negative views about menstruation at quite a young age. Even more disturbing is the fact that early menarche can serve as a rough predictor for increased risk for eating disorders[4]. This seemed to reinforce the fact that girls need support and positive reinforcement from their physicians about the facts of menstruation and the normality of the experience.

The medical students' workshop was designed to heighten their awareness of menstruation as it presents in clinical practice with attention to the emotional, social and cultural contexts of menstruation. The workshop began with a case that included issues such as early menarche, exercising during menstruation, menstrual product options and body image. The students were asked to identify issues in the case and suggest ways of addressing them. After this opening discussion, we outlined the scope of the honours PBL project and then cited some of the findings from our search of the literature. We discussed the psychological framework of the adolescent girl and the complexities that formed the foundation for menarcheal and menstrual experiences. The social context of menstruation was reviewed in terms of the media's presentation of menstruation in advertising and common social myths. A collage of advertisements depicting various menstrual products was circulated to illustrate the common themes of: ideals of femininity, the promotion of cleanliness and conversely dirtiness of menstruation.

We also mentioned some of the cultural and religious contexts of menstruation and how they can impact upon women's experiences. An example is the orthodox Jewish tradition of a ceremonial cleansing bath, the Mikvah. In addition we elicited from the students some of the myths they had heard about menstruation such as women not being able to swim during their periods. We also spent some time talking about girls who undergo early menarche, experience dysmenorrhea or premenstrual syndrome symptoms. The session was concluded by a summary of what girls need to know about menstruation from their physicians (Table 2). At the end of the workshop, we handed out the same pamphlet that the young girls received so that the medical students could use it as a reference for their patients.

We received a lot of positive feedback from the medical students in Meds 2000 and Meds 2001 who attended the workshop. In particular, the male medical students seemed to feel it was particularly beneficial to learn about some of the practical issues surrounding menstruation. They believed this would help them feel more comfortable talking to their female patients about menstruation. In the evaluation phase of our project, Dr. Barbara Lent, a family physician at the Victoria Medical Center, approached us about presenting the medical student workshop with family medicine residents. During one of the noon hour Family Medicine rounds at Victoria Medical Center, we presented the workshop and it was well received with active participation and discussion.

Table 2
What girls need to know about menstruation from their physicians

- Menstrual physiology
- Menstrual hygiene
- The normality of menstruation — it must be distinguished from disease, injury, and uncleanliness
- Feelings of fright and embarrassment girls experience at menarche must be acknowledged as normal
- Negative aspects of menstruation (eg. PMS, menstrual cramps, inconvenience) need to be discussed in order to provide a balanced view
- Girls need support and reassurance at the time of menarche
- Families need to be prepared to be informed, understanding, and accepting
- It is important to find out where girls have obtained their information about menstruation and question the accuracy of the source if necessary

CONCLUSION

For an idea that began as a high school experience, "Sharing Information with Young Girls about Menstruation" expanded into a project that encompassed a wide range of issues. There is evidence to support the impact of educational intervention on a girl's menstrual experiences. Armed with this information, we were able to develop an innovative workshop that had a positive impact on a group of young girls. Furthermore, we were able to encourage future physicians to engage in similar interactive discussions with their young patients. Given that the non-biological issues of menstruation are often overlooked in medicine, it is our hope that with this project and this article we may give more health care providers reason to consider them more carefully in their patients.

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INDICATIONS AND CLINICAL USE

Synthroid (Levothyroxine sodium) is indicated:

1. As replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis; primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of the thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism (see **CONTRAINDICATIONS** and **PRECAUTIONS**). Synthroid Injection can be used intravenously when rapid repletion is required, and either intravenously or intramuscularly when the oral route is precluded.
2. As a pituitary TSH suppressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter, and in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

CONTRAINDICATIONS

Synthroid (Levothyroxine sodium) is contraindicated in patients with untreated thyrotoxicosis of any etiology, acute myocardial infarction, or an apparent hypersensitivity to thyroid hormones or any of the inactive product constituents. (Note: The 50 mcg tablet is formulated without colour additives for patients who are sensitive to dyes.) There is no well-documented evidence of true allergic or idiosyncratic reactions to thyroid hormone. Synthroid is also contraindicated in patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis (see **PRECAUTIONS**).

WARNINGS

Thyroid hormones, either alone or together with other therapeutic agents, should not be used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

The use of Synthroid (Levothyroxine sodium) in the treatment of obesity, either alone or in combination with other drugs, is unjustified. The use of Synthroid is also unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

PRECAUTIONS

General:

Synthroid (Levothyroxine sodium) should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, and hypertension, and in the elderly who have a greater likelihood of occult cardiac disease. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Use of Synthroid in patients with concomitant diabetes mellitus, diabetes insipidus or adrenal cortical insufficiency may aggravate the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases may therefore be required. Treatment of myxedema coma may require simultaneous administration of glucocorticoids (see **DOSAGE AND ADMINISTRATION**).

T_4 enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both Synthroid and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly.

The bioavailability of levothyroxine may differ to some extent among marketed brands. Once the patient is stabilized on a particular brand of levothyroxine sodium, caution should be exercised when a change in drug product brand is implemented.

It has been shown that differences in formulations of levothyroxine, despite an identical content of active ingredient, may be associated with differences in fractional gastrointestinal absorption. These differences may not be observed through measurement of total T_3 and T_4 serum levels. It is therefore, recommended that patients who are switched from one levothyroxine formulation to another be retitrated to the desired thyroid function. Accuracy in retitration can best be achieved by using sensitive thyrotropin assays.

The intestinal absorption of levothyroxine may be impaired in patients with absorption disorder; in such patients, higher dosage levels of levothyroxine may be required.

Seizures have been reported rarely in association with the initiation of levothyroxine sodium therapy, and may be related to the effect of thyroid hormone on seizure threshold.

Lithium blocks the TSH-mediated release of T_4 and T_3. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual Synthroid dose may be required.

Information for the Patient:

1. Synthroid is intended to replace a hormone that is normally produced by your thyroid gland. It is generally taken for life, except in cases of temporary hypothyroidism associated with an inflammation of the thyroid gland.
2. Before or at any time while using Synthroid you should tell your doctor if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding, are taking or start taking any other prescription or nonprescription (OTC) medications, or have any other medical problems (especially hardening of the arteries, heart disease, high blood pressure, or history of thyroid, adrenal or pituitary gland problems).
3. Use Synthroid only as prescribed by your doctor. Do not discontinue Synthroid or change the amount you take or how often you take it, except as directed by your doctor.
4. Synthroid, like all medicines obtained from your doctor, must be used only by you and for the condition determined appropriate by your doctor.
5. It may take a few weeks for Synthroid to begin working. Until it begins working, you may not notice any change in your symptoms.
6. You should notify your doctor if you experience any of the following symptoms, or if you experience any other unusual medical event: chest pain, shortness of breath, hives or skin rash, rapid or irregular heartbeat, headache, irritability, nervousness, sleeplessness, diarrhea, excessive sweating, heat intolerance, changes in appetite, vomiting, weight gain or loss, changes in menstrual periods, fever, hand tremors, leg cramps.
7. You should inform your doctor or dentist that you are taking Synthroid before having any kind of surgery.
8. You should notify your doctor if you become pregnant while taking Synthroid. Your dose of this medicine will likely have to be increased while you are pregnant.
9. If you have diabetes, your dose of insulin or oral antidiabetic agent may need to be changed after starting Synthroid. You should monitor your blood or urinary glucose levels as directed by your doctor and report any changes to your doctor immediately.
10. If you are taking an oral anticoagulant drug such as warfarin, your dose may need to be changed after starting Synthroid. Your coagulation status should be checked often to determine if a change in dose is required.
11. Partial hair loss may occur rarely during the first few months of Synthroid therapy, but it is usually temporary.
12. Synthroid is the trade name for tablets containing the thyroid hormone levothyroxine sodium, manufactured by Knoll Pharma Inc. Other manufacturers also make tablets containing levothyroxine. Neither you nor your pharmacist should change to another manufacturer's product without discussing that change with your doctor first. Repeat blood tests and a change in the amount of levothyroxine you take may be required.
13. Keep Synthroid out of the reach of children. Store Synthroid away from heat, light and moisture.

Laboratory Tests:

Treatment of patients with Synthroid requires periodic assessment of thyroid status by appropriate laboratory tests and clinical evaluation. Selection of appropriate tests for the diagnosis and management of thyroid disorders depends on patient variables such as presenting signs and symptoms, pregnancy, and concomitant medications. A combination of sensitive TSH assay and free T_4 estimate (free T_4 index, FT_4 I) are recommended to confirm a diagnosis of thyroid disease. Normal ranges for these parameters are age-specific in newborns and younger children.

TSH alone or initially may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and free T_4. Measurement of total serum T_4 and T_3, resin T_3 uptake, and free T_3 concentrations may also be useful. Antithyroid microsomal antibodies are an indicator of autoimmune thyroid disease. Positive microsomal antibody presence in an euthyroid patient is a major risk factor for the development of hypothyroidism. An elevated serum TSH in the presence of a normal T_4 may indicate subclinical hypothyroidism. Intracellular resistance to thyroid hormone is quite rare, and is suggested by clinical signs and symptoms of hypothyroidism in the presence of high serum T_4 levels. Adequacy of Synthroid therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free T_4, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition. Adequacy of Synthroid therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring serum total T_4 or free T_4; these should be maintained in the upper half of the normal range. In congenital hypothyroidism, serum TSH normalization may lag behind serum T_4 normalization by 2 to 3 months or longer. In rare patients, serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal T_4 or free T_4 levels. (See **Pediatric use**.)

Drug Interactions:

The magnitude and relative clinical importance of the effects noted below are likely to be patient-specific and may vary by such factors as age, gender, race, intercurrent illnesses, dose of either agents, additional concomitant medications, and timing of drug administration. Any agent that alters thyroid hormone synthesis, secretion, distribution, effect on target tissues, metabolism, or elimination may alter the optimal therapeutic dose of Synthroid.

Levothyroxine sodium absorption – The following agents may bind and decrease absorption of levothyroxine sodium from the gastrointestinal tract: aluminum hydroxide, cholestyramine resin, colestipol hydrochloride, ferrous sulfate, sodium polystyrene sulfonate, soybean flour (e.g., infant formula), sucralfate.

Binding to serum proteins – The following agents may either inhibit levothyroxine sodium binding to serum proteins or alter the concentrations of serum binding proteins: androgens and related anabolic hormones, asparaginase, clofibrate, estrogens and estrogen-containing compounds, 5-fluorouracil, furosemide, glucocorticoids, meclofenamic acid, mefenamic acid, methadone, perphenazine, phenylbutazone, phenytoin, salicylates, tamoxifen.

Thyroid physiology – The following agents may alter thyroid hormone or TSH levels, generally by effects on thyroid hormone synthesis, secretion, distribution, metabolism, hormone action, or elimination, or altered TSH secretion: aminoglutethimide, p-aminosalicylic acid, amiodarone, androgens and related anabolic hormones, complex anions (thiocyanate, perchlorate, pertechnetate), antithyroid drugs, ß-adrenergic blocking agents, carbamazepine, chloral hydrate, diazepam, dopamine and dopamine agonists, ethionamide, glucocorticoids, heparin, hepatic enzyme inducers, insulin, iodinated cholestographic agents, iodine-containing compounds, levodopa, lovastatin, lithium, 6-mercaptopurine, metoclopramide, mitotane, nitroprusside, phenobarbital, phenytoin, resorcinol, rifampin, somatostatin analogs, sulfonamides, sulfonylureas, thiazide diuretics.

Adrenocorticoids – Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients, and may therefore change with changing thyroid status.

Amiodarone – Amiodarone therapy alone can cause hypothyroidism or hyperthyroidism.

Anticoagulants (oral) – The hypoprothrombinemic effect of anticoagulants may be potentiated, apparently by increased catabolism of vitamin K-dependent clotting factors.

Antidiabetic agents (insulin, sulfonylureas) – Requirements for insulin or oral antidiabetic agents may be reduced in hypothyroid patients with diabetes mellitus, and may subsequently increase with the initiation of thyroid hormone replacement therapy.

ß-adrenergic blocking agents – Actions of some beta-blocking agents may be impaired when hypothyroid patients become euthyroid.

Cytokines (interferon, interleukin) – Cytokines have been reported to induce both hyperthyroidism and hypothyroidism.

Digitalis glycosides – Therapeutic effects of digitalis glycosides may be reduced. Serum digitalis levels may be decreased in hyperthyroidism or when a hypothyroid patient becomes euthyroid.

Ketamine – Marked hypertension and tachycardia have been reported in association with concomitant administration of levothyroxine sodium and ketamine.

Maprotiline – Risk of cardiac arrhythmias may increase.

Sodium iodide (^{123}I) and ^{131}I), sodium pertechnetate Tc99m – Uptake of radiolabeled ions may be decreased.

Somatrem/somatropin – Excessive concurrent use of thyroid hormone may accelerate epiphyseal closure. Untreated hypothyroidism may interfere with the growth response to somatrem or somatropin.

Theophylline – Theophylline clearance may decrease in hypothyroid patients and returns toward normal when the euthyroid state is achieved.

Tricyclic antidepressants – Concurrent use may increase the therapeutic and toxic effects of both drugs, possibly due to increased catecholamine sensitivity. Onset of action of tricyclics may be accelerated.

Sympathomimetic agents – Possible increased risk of coronary insufficiency in patients with coronary artery disease.

Laboratory Test Interactions:

A number of drugs or moieties are known to alter serum levels of TSH, T_4 and T_3 and may thereby influence the interpretation of laboratory tests of thyroid function (see **Drug Interactions**).

1. Changes in TBG concentration should be taken into consideration when interpreting T_4 and T_3 values. Drugs such as estrogens and estrogen-containing oral contraceptives increase serum TBG concentrations. TBG concentrations may also be increased during pregnancy and in infectious hepatitis. Decreases in TBG concentrations are observed in nephrosis, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxine-binding- globulinemias have been described. The incidence of TBG deficiency is approximately 1 in 9000. Certain drugs such as salicylates inhibit the protein-binding of T_4. In such cases, the unbound (free) hormone should be measured. Alternatively, an indirect measure of free thyroxine, such as the FT_4 I, may be used.
2. Medicinal or dietary iodine interferes with in vivo tests of radioiodine uptake, producing low uptakes which may not indicate a true decrease in hormone synthesis.
3. Persistent clinical and laboratory evidence of hypothyroidism despite an adequate replacement dose suggests either poor patient compliance, impaired absorption, drug interactions, or decreased potency of the preparation due to improper storage.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T_4 is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving Synthroid for established indications should not discontinue therapy.

Pregnancy:

Studies in pregnant women have not shown that Synthroid increases the risk of fetal abnormalities if administered during pregnancy. If Synthroid is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, Synthroid should be used during pregnancy only if clearly needed.

Thyroid hormones cross the placental barrier to some extent. T_4 levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T_4 may not prevent in utero hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion and preeclampsia, and has been reported to have an adverse effect on fetal and childhood development. On the basis of current knowledge, Synthroid should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T_4 concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as 4 weeks gestation.

Pregnant women who are maintained on Synthroid should have their TSH measured periodically. An elevated TSH should be corrected by an increase in Synthroid dose. After pregnancy, the dose can be decreased to the optimal preconception dose.

Nursing Mothers:

Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have known tumorigenic potential. While caution should be exercised when Synthroid is administered to a nursing woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

Pediatric Use:

Congenital hypothyroidism: Rapid restoration of normal serum T_4 concentrations is essential to prevent dele-

terious neonatal thyroid hormone deficiency effects on intelligence, overall growth, and development. Treatment should be initiated immediately upon diagnosis and generally maintained for life. The therapeutic goal is to maintain serum total T_4 or FT_4 in the upper half of the normal range and serum TSH in the normal range.

An initial starting dose of 10 to 15 mcg/kg/day (ages 0-3 months) will generally increase serum T_4 concentrations to the upper half of the normal range in less than 3 weeks. Clinical assessment of growth, development, and thyroid status should be monitored frequently. In most cases, the Synthroid dose per body weight will decrease as the patient grows through infancy and childhood (see **DOSAGE AND ADMINISTRATION, Pediatric Dosage, Table 1**). Prolonged use of large doses in infants may be associated with temperament problems, which appear to be transient.

Thyroid function tests (serum total T_4 or FT_4, and TSH) should be monitored closely and used to determine the adequacy of Synthroid therapy. Serum T_4 normalization is usually followed by a rapid decline in TSH. Nevertheless, TSH normalization may lag behind T_4 normalization by 2 to 3 months or longer. The relative serum TSH elevation is more marked in the early months, but can persist to some degree throughout life. In rare patients TSH remains relatively elevated despite clinical euthyroidism and age-specific normal total T_4 or FT_4 levels. Increasing the Synthroid dosage to suppress TSH into the normal range may produce overtreatment, with an elevated serum T_4 and clinical features of hyperthyroidism including: irritability, increased appetite with diarrhea, and sleeplessness. Another risk of prolonged overtreatment in infants is premature cranial synostosis.

Hypothyroidism permanence may be assessed when transient hypothyroidism is suspected. Levothyroxine therapy may be interrupted for 30 days after three years of age and serum T_4 and TSH measured. Low T_4 and elevated TSH confirms permanent hypothyroidism; therapy should be re- instituted. If T_4 and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic thyroid function test reevaluation may be warranted.

Acquired hypothyroidism: The initial Synthroid dose varies with age and body weight, and should be adjusted to maintain serum total T_4 or free T_4 levels in the upper half of the normal range. In general, unless there are overriding clinical concerns, children should be started on a full replacement dose. Children with underlying heart disease should be started at lower dosages, with careful upward titration. Children with severe, longstanding hypothyroidism may also be started on a lower initial dose followed by an upward titration, attempting to avoid premature epiphyseal closure. The recommended dose per body weight decreases with age (see **DOSAGE AND ADMINISTRATION, Pediatric Dosage, Table 1**).

Treated children may resume growth at a greater than normal rate (period of transient catch-up growth). In some cases the catch-up may be adequate to normalize growth. However, severe and prolonged hypothyroidism may reduce adult height. Excessive thyroxine replacement may initiate accelerated bone maturation, producing disproportionate skeletal age advancement and shortened adult stature.

Hypothyroidism permanence may assessed when transient hypothyroidism is suspected. Levothyroxine therapy may be interrupted for 30 days and serum T_4 and TSH measured. Low T_4 and elevated TSH confirms permanent hypothyroidism; therapy should be re-instituted. If T_4 and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic thyroid function test reevaluation may be warranted.

ADVERSE REACTIONS

Adverse reactions other than those indicative of thyrotoxicosis as a result of therapeutic overdosage, either initially or during the maintenance periods, are rare (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**). Craniosynostosis has been associated with iatrogenic hyperthyroidism in infants receiving thyroid hormone replacement therapy. Inadequate doses of Synthroid (levothyroxine sodium) may produce or fail to resolve symptoms of hypothyroidism. Hypersensitivity reactions to the product excipients, such as rash and urticaria, may occur. Partial hair loss may occur during the initial months of therapy, but is generally transient. The incidence of continued hair loss is unknown. Pseudotumour cerebri has been reported in pediatric patients receiving thyroid hormone replacement therapy.

DOSAGE AND ADMINISTRATION

The dosage and rate of administration of Synthroid (Levothyroxine sodium) is determined by the indication, and must in every case be individualized according to patient response and laboratory findings.

Adult Dosage:

Hypothyroidism:

The goal of therapy for primary hypothyroidism is to achieve and maintain a clinical and biochemical euthyroid state with consequent resolution of hypothyroid signs and symptoms. The starting dose of Synthroid, the frequency of dose titration, and the optimal full replacement dose must be individualized for every patient, and will be influenced by such factors as age, weight, cardiovascular status, presence of other illness, and the severity and duration of hypothyroid symptoms.

The usual full replacement dose of Synthroid for younger, healthy adults is approximately 1.6 mcg/kg/day administered once daily. In the elderly, the full replacement dose may be altered by decreases in T_4 metabolism and levothyroxine sodium absorption. Older patients may require less than 1 mcg/kg/day. Children generally require higher doses (see **Pediatric Dosage**). Women who are maintained on Synthroid during pregnancy may require increased doses (see **PRECAUTIONS – Pregnancy**).

Therapy is usually initiated in younger, healthy adults at the anticipated full replacement dose. Clinical and laboratory evaluations should be performed at 6 to 8 week intervals (2 to 3 weeks in severely hypothyroid patients), and the dosage adjusted by 12.5 to 25 mcg increments until the serum TSH concentration is normalized and signs and symptoms resolve. In older patients or in younger patients with a history of cardiovascular disease, the starting dose should be 12.5 to 50 mcg once daily with adjustments of 12.5 to 25 mcg every 3 to 6 weeks until TSH is normalized. If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the dose of Synthroid reduced. Rarely, worsening angina or other signs of cardiac ischemia may prevent achieving a TSH in the normal range.

Treatment of subclinical hypothyroidism may require lower than usual replacement doses, e.g. 1.0 mcg/kg/day. Patients for whom treatment is not initiated should be monitored yearly for changes in clinical status, TSH, and thyroid antibodies.

In patients with hypothyroidism resulting from pituitary or hypothalamic disease, the possibility of secondary adrenal insufficiency should be considered, and if present, treated with glucocorticoids prior to initiation of Synthroid. The adequacy of Synthroid therapy should be assessed in these patients by measuring FT_4I, which should be maintained in the upper half of the normal range, in addition to clinical assessment. Measurement of TSH is not a reliable indicator of response to therapy for this condition.

Few patients require doses greater than 200 mcg/day. An inadequate response to daily doses of 300 to 400 mcg/day is rare, and may suggest malabsorption, poor patient compliance, and/or drug interactions.

Once optimal replacement is achieved, clinical and laboratory evaluations should be conducted at least annually or whenever warranted by a change in patient status. Levothyroxine sodium products from different manufacturers should not be used interchangeably unless retesting of the patient and retitration of the dosage, as necessary, accompanies the product switch.

Synthroid Injection by the intravenous or intramuscular route can be substituted for the oral dosage form when rapid repletion is required or oral administration is precluded. The initial parenteral dosage should be approximately one-half the previously established oral dosage of Synthroid Tablets. Close observation of the patient is recommended, with adjustment of the dosage as needed. Administration of Synthroid Injection by the subcutaneous route is not recommended as studies have shown that the influx of T_4 from the subcutaneous site is very slow, and depends on many factors such as volume of injection, the anatomic site of injection, ambient temperature, and presence of venospasm.

Myxedema Coma:

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a medical emergency. It is characterized by hypothermia, hypotension, hypoventilation, hyponatremia, and bradycardia. In addition to restoration of normal thyroid hormone levels, therapy should be directed at the correction of electrolyte disturbances and possible infection. Because the mortality rate of patients with untreated myxedema coma is high, treatment must be started immediately, and should include appropriate supportive therapy and corticosteroids to prevent adrenal insufficiency. Possible precipitating factors should also be identified and treated. Synthroid may be given via nasogastric tube, but the preferred route of administration is intravenous. A bolus dose of Synthroid is given immediately to replete the peripheral pool of T_4, usually 300 to 500 mcg. Although such a dose is usually well-tolerated even in the elderly, the rapid intravenous administration of large doses of Synthroid to patients with cardiovascular disease is clearly not without risks. Under such circumstances, intravenous therapy should not be undertaken without weighing the alternate risks of myxedema coma and the cardiovascular disease. Clinical judgement in this situation may dictate smaller intravenous doses of Synthroid. The initial dose is followed by daily intravenous doses of 75 to 100 mcg until the patient is stable and oral administration is feasible. Normal T_4 levels are usually achieved in 24 hours, followed by progressive increases in T_3. Improvement in cardiac output, blood pressure, temperature, and mental status generally occur within 24 hours, with improvement in many manifestations of hypothyroidism in 4 to 7 days.

TSH Suppression in Thyroid Cancer and Thyroid Nodules:

The rationale for TSH suppression therapy is that a reduction in TSH secretion may decrease the growth and function of abnormal thyroid tissue. Exogenous thyroid hormone may inhibit recurrence of tumour growth and may produce regression of metastases from well-differentiated (follicular and papillary) carcinoma of the thyroid. It is used as ancillary therapy of these conditions following surgery or radioactive iodine therapy. Medullary and anaplastic carcinoma of the thyroid is unresponsive to TSH suppression therapy. TSH suppression is also used in treating nontoxic solitary nodules and multinodular goiters.

No controlled studies have compared the various degrees of TSH suppression in the treatment of either benign or malignant thyroid nodular disease. Further, the effectiveness of TSH suppression for benign nodular disease is controversial. The dose of Synthroid used for TSH suppression should therefore be individualized by the nature of the disease, the patient being treated, and the desired clinical response, weighing the potential benefits of therapy against the risks of iatrogenic thyrotoxicosis. In general, Synthroid should be given in the smallest dose that will achieve the desired clinical response.

For well-differentiated thyroid cancer, TSH is generally suppressed to less than 0.1 mU/L. Doses of Synthroid greater than 2 mcg/kg/day are usually required. The efficacy of TSH suppression in reducing the size of benign thyroid nodules and in preventing nodule regrowth after surgery is controversial. Nevertheless, when treatment with Synthroid is warranted, TSH is generally suppressed to a higher target range (e.g., 0.1 to 0.3 mU/L) than that employed for the treatment of thyroid cancer. Synthroid therapy may also be considered for patients with nontoxic multinodular goiter who have a TSH in the normal range, to moderately suppress TSH (e.g., 0.1 to 0.3 mU/L).

Synthroid should be administered with caution to patients in whom there is a suspicion of thyroid gland autonomy, in view of the fact that the effects of exogenous hormone administration will be additive to endogenous thyroid hormone production.

Pediatric Dosage:

Congenital or acquired hypothyroidism: The Synthroid pediatric dosage varies with age and body weight. Synthroid should be given at a dose that maintains T_4 or free T_4 in the upper half of the normal range and serum TSH in the normal range (See **PRECAUTIONS, Pediatric Use.**) Normalization of TSH may lag significantly behind T_4 in some infants. In general, despite the smaller body size of children, the dosage (on a weight basis) required to sustain full development and general thriving is higher than in adults. See Table 1.

Therapy is usually initiated at the full replacement dose (see Table 1). Infants and neonates with very low (< 5 mcg/dL) or undetectable serum T_4 levels should be started at higher end of the dosage range (e.g.50 mcg daily). A lower dose (e.g., 25 mcg daily) should be considered for neonates at risk of cardiac failure, increasing every few days until a full maintenance dose is reached. In children with severe, longstanding hypothyroidism, Synthroid should be initiated gradually, with an initial 25 mcg dose for two weeks, then increasing by 25 mcg every 2 to 4 weeks until the desired dose, based on serum T_4 and TSH levels, is achieved.

Table 1: **Dosage Guidelines for Pediatric Hypothyroidism**

Age	Daily dose (mcg) per kg of body weight *
0 - 3 months	10 - 15
3 - 6 months	8 - 10
6 - 12 months	6 - 8
1 - 5 years	5 - 6
6 - 12 years	4 - 5
> 12 years	2 - 3
Growth and puberty complete	1.6

*To be adjusted on the basis of clinical response and laboratory tests (see **PRECAUTIONS, Pediatric use**).

Serum T_4 and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustments to normalize serum total T_4 or FT_4 and TSH:

2 and 4 weeks after therapy initiation,
every 1 to 2 months during the first year of life,
every 2 to 3 months between 1 and 3 years of age,
every 3 to 12 months thereafter until growth is completed

Evaluation at more frequent intervals is indicated when compliance is questioned or abnormal laboratory values are obtained. Patient evaluation is also advisable approximately 6 to 8 weeks after any change in Synthroid dose.

Synthroid Tablets may be given to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount of water (5 to 10 mL), breast milk or non-soybean based formula. The suspension can be given by spoon or dropper. DO NOT STORE THE SUSPENSION FOR ANY PERIOD OF TIME. The crushed tablet may also be sprinkled over a small amount of food, such as apple sauce. Foods or formula containing large amounts of soybean, fibre, or iron should not be used for administering Synthroid.

AVAILABILITY

Synthroid® (Levothyroxine sodium) Tablets: round, colour coded, scored tablet debossed with "FLINT" and potency. Synthroid Tablets contain the following inactive ingredients: acacia, confectioner's sugar, lactose, magnesium stearate, povidone and talc. The strengths available and the colour additives by tablet strength are as follows:

Strength (mcg)	Tablet Colour	Colour Additive(s)
25	orange	FD&C Yellow No. 6
50	white	none
75	violet	FD&C Red No. 40 FD&C Blue No. 2
88	olive	FD&C Blue No. 1 FD&C Yellow No. 6 D&C Yellow No. 10
100	yellow	D&C Yellow No. 10 FD&C Yellow No. 6
112	rose	D&C Red No. 27 & 30
125	brown	FD&C Yellow No. 6 FD&C Red No. 40 FD&C Blue No. 1
150	blue	FD&C Blue No. 2
175	lilac	FD&C Blue No. 1 D&C Red. No. 27 & 30
200	pink	FD&C Red No. 40
300	green	D&C Yellow No. 10 FD&C Yellow No. 6 FD&C Blue No. 1

All strengths are available in bottles of 100 tablets each; 50, 75, 100, 125, 150, 200 and 300 mcg strengths are also available in bottles of 1000 tablets each.

Store at controlled room temperature 15°– 30°C (59°–86°F). Synthroid Tablets should be protected from light and moisture.

Synthroid® (Levothyroxine sodium) Injection is a lyophilized powder. Inactive ingredients include: 10 mg Mannitol, USP, sodium hydroxide, 1.75 mg tribasic sodium phosphate, anhydrous. Levothyroxine sodium powder for reconstitution for injection is a sterile preparation. It is supplied in a 10 mL single dose colour-coded (yellow) vial containing 500 mcg levothyroxine sodium, USP. Store at controlled room temperature 15°– 30°C (59°– 86°F).

Directions for Reconstitution: Reconstitute the lyophilized levothyroxine sodium by aseptically adding 5 mL of 0.9% Sodium Chloride Injection, USP only. DO NOT USE BACTERIOSTATIC SODIUM CHLORIDE INJECTION, USP, AS THE BACTERIOSTATIC AGENT MAY INTERFERE WITH COMPLETE RECONSTITUTION. Shake vial to ensure complete mixing. Use immediately after reconstitution. Do not add to other intravenous fluids. Discard any unused portion.

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RECOGNITION AND MANAGEMENT OF THE ABUSED WOMAN IN THE EMERGENCY DEPARTMENT

By Jim Grochowski, MEDS 2000

Treating victims of domestic violence has always been part of emergency room work. Major emergency departments offer 24-hour access and relative anonymity for victims of domestic violence. Emergency room staff occupy a unique position in the health care system and are strategically positioned to effectively intervene in the abuse of a woman by her partner. Although the ER is often a woman's first opportunity for disclosure of abuse, a literature review revealed criticism of current management of battered women.

This article will review current knowledge on domestic violence, effective screening processes, useful assessment techniques, the development of a safety plan and available support services in the community.

EPIDEMIOLOGY OF DOMESTIC ABUSE

In 1993, Statistics Canada estimated that 25% of Canadian women who have been married or lived common-law have been assaulted by their partner.[1] It is difficult to obtain accurate data on this crime because of significant underreporting and the exclusion of couples who do not meet the legal definition of marriage/common-law.[2] The problem is likely much more serious.[1,3] In Ontario, 87% of those charged with domestic violence are men.[3] The author acknowledges that men too can be victims of domestic abuse but this article will only discuss female victims.

Socio-economic status, ethnicity, sexual orientation and pregnancy offer no exemption from experiences of abuse to women.[3] It has been reported that for 40% of abused women the abuse begins during pregnancy and 39% of women report that their children witness the violence.[1] It is known that children who grow up where there is spousal abuse are more likely to be in violent relationships when they are adults and the risk of being an abuser is three times higher for men who witnessed violence by their fathers.[1] It should be clear then that domestic violence is not an individual problem but instead a societal issue that affects us all.

Over 20% of women who use the emergency room are battered women and almost half of the injuries sustained by women who present to the ER are the result of domestic violence.[1,4] The abuse is not an isolated incident in 2/3 of the cases.[1] Forty percent of abused women seek medical attention on at least five different occasions.[2] There clearly exists an excellent opportunity by emergency room physicians and staff for intervention in domestic abuse.

ABOUT THE AUTHOR

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ABUSE

Woman abuse is defined as the intentional and systematic use of tactics to establish and maintain power and control over the thoughts, beliefs and conduct of a woman.[3] Abuse can be physical, sexual, psychological/emotional and financial in nature.[3] It can involve intimidation, isolation, and threats, using the children and using social status.[3] The Power and Control Wheel in Figure 1, adapted by the London Battered Women's Advocacy Centre, London, Ontario, from the Domestic Abuse Intervention Project, Duluth, MN, is a useful tool for understanding the various forms of abuse. The intentional nature of the abuse is confirmed by the shifting of abuse tactics according to what abusers believe will work in a given situation, the mood they are in and the response they are looking for from their partner.[3] The tactics may appear to be random and inexplicable, but become fully explainable in the context of the abuser attempting to establish power in a relationship.

Emotional and psychological consequences of abuse have been identified by abused women as being far more damaging then the physical assault itself.[5] Emotional abuse kills the spirit, and prevents the woman from succeeding later in life, to feel deeply and to make emotional contact with others.[6] In fact, battering accounts for 1 in every 4 suicide attempts by women.[2] All forms of abuse result in the loss of dignity, control and safety, and the feeling of powerlessness and entrapment.[3]

Tactics of control can begin very slowly as coercive tactics that may not be criminal in nature.[3] This makes it far more difficult for the women, as well as friends, family, or professionals to recognize it as abuse.[3] Physicians should keep in mind that abusers often can present themselves as charming. This could influence a physician's assessment.[7] Abuse typically escalates in frequency and severity and once abusers use physical violence, they are likely to intensify the abuse.[3]

INTERDISCIPLINARY HEALTH CARE TEAM

Coordination among health care professionals is paramount to developing a consistent and interdisciplinary health care team. A study by *Shields et al.* showed that when physicians, nurses, and social workers collaborated, the outcome appeared to be more comprehensive, and the emotional symptoms of the

abused woman were more likely to be discussed.[8] It has also been found that an interdisciplinary team approach heightens the professional expertise of each member.[8]

The emergency room nurse is the abused woman's first contact with the health care system. In many cases, it is a nurse who brings suspected cases of domestic abuse to the attention of the physician.[8] When a patient indicates she is being abused, referral to a social worker for further assessment is extremely important. Other health care providers can assist the team by maintaining a non-judgmental attitude.[8]

DOMESTIC VIOLENCE SCREENING

A study in 1987 suggested that the detection of domestic violence in the emergency department resulted in only one abused woman in twenty-five diagnosed.[2] More recently, routine screening has been shown to be effective in identifying abused women.[9] It has been suggested that physicians routinely ask all patients about the possibility of domestic violence.[3] However, a survey in 1994 suggests this is not occurring; only 13% of 198 Canadian hospitals surveyed said universal screening was part of the ER protocol.[10]

A physician should always ask about the possibility of abuse in cases when a woman's physical injuries are not consistent with her explanation for them; if there is unexpected or unexplainable stress, anxiety, depression, or substance abuse; or if there are chronic unexplained symptoms.[7] Table 1 is a summary of cues which may lead to an increased level of suspicion for domestic abuse.

Women confide mostly in friends, neighbours and family (44%) about being abused; only 25% of abused women tell a doctor.[1] A study by Hayden et al. showed that 89% of abused women surveyed would feel comfortable in disclosing the abuse to health care professionals if asked.[12] Placing posters about domestic violence in the waiting room, washrooms, and examination rooms is recommended in emergency departments and indicates an openness to the discussion of abuse.[7] Screening should be done with the woman alone in a private area.[3] Occasionally, her partner refuses to leave her side and this can present a problem for screening. The nursing staff should be informed of the suspicion of abuse and the attempt that is being made to separate the patient from the partner. One technique successfully used in the emergency room is to tell the patient and her partner that x-rays will be needed (radiographs are not actually done unless necessary).[13] The physician can then meet the patient later in the x-ray department and screening can be done without the intimidating presence of her

Table 1—Raising the Level of Suspicion of Domestic Abuse [2, 3, 7, 11]

These cues should alert a physician to the possibility of abuse and prompt the initiation of direct screening:

1) Frequent use of emergency department (typically 5pm-4am; though some women may wait until the next day when their children are in school)
2) Recurrent trauma history with injuries especially to the head, neck, torso, breasts, abdomen or genitals.
3) Abrasions and contusions are more commonly seen in battered women.
4) Physical injuries that are multi-site and bilateral do not normally occur in accidents.
5) Delay in seeking medical treatment.
6) Signs of old untreated injuries.
7) Behavioural cases such as depression, suicidal ideation, anxiety, sleep disorders, panic attacks, symptoms of post traumatic stress disorder, substance abuse problems, chronic headaches and chronic pain of no apparent etiology.
8) A partner who seems over protective answers for the woman or will not leave her side.

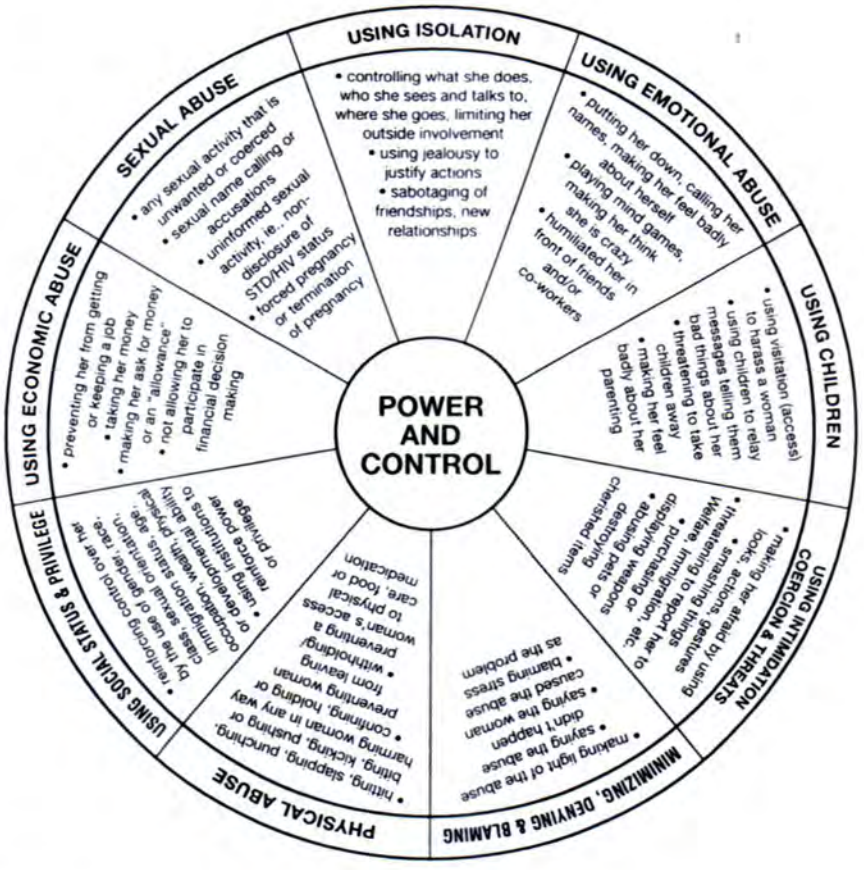

Figure 1
Power and Control Wheel used by London Battered Women's Advocacy Centre, London, Ontario.

Table 2—Screening [2, 3, 13, 14]

1) Screen alone in a safe environment.
2) Use a non-threatening, non-judgmental approach.
3) Build trust and rapport by making good eye contact with the patient.
4) Use questions that are direct and easy to understand.
5) If the woman does not speak English, do not use family members or a person known to her; use a professional fluent in her language.
6) Use a leading statement such as: "Because violence is so common in so many women's lives, I've begun to ask about it routinely." Or "We have seen many women with similar complaints and injuries presenting to the emergency department, and some are victims of violence at home."
7) Follow up with more specific questions: "I am concerned that your injuries have come from someone hurting you, is this what happened to you?", "Have you ever been hurt or hit by someone close to you?", "I notice you have some bruising or your breasts and abdomen. Can you tell me what happened? Did somebody hit you?"
8) Use the word "partner" if the abuser's gender is unknown.
9) Respect that she may refuse to give information or receive help.
10) Regardless of outcome, record that abuse screening was done.

Table 3-Signs of Physical Abuse on Physical Exam [3, 15]

1) Injuries (often multiple) found on head, face, throat, chest, breasts, back, abdomen, genitals.
2) The following types of injuries: abrasions, bruises, burns, dislocations, lacerations, bites, fractures (nose, jaw, clavicle, ribs, arms, fingers), strangulation.
3) Evidence of old bruising and radiographic suggestion of past fractures.
4) Soreness and general body pain from being hurled or shoved.
5) Unusual affect or manner of communication – she says nothing, minimizes the injury, avoids eye contact, anxious about a minor injury.

Table 4 - Creating a Safety Plan [3, 4, 6]

A safety plan should include:
1) Asking what she wants to do, whether she can stay with friends/family or go to a shelter.
2) A list of resources and brochures (wallet-sized) which contain emergency phone number (police, hospitals, shelters and help lines) and the location of nearby shelters.
3) Information about educational services, legal and/or immigration assistance.
4) Suggest she alert a supportive family member or friend of her situation.
5) Prepare an escape package by having her gather the following items and keep them in an accessible hidden place or at a friend's home in case she has to leave in a hurry: important documents, some money/bank or credit cards, clothing for herself and children, plus the child's favourite toy.

partner. Table 2 provides a summary of screening techniques and examples of ways to approach the question of abuse.

The victim must first come to understand that what is happening constitutes abuse, then to see that it is unacceptable, and finally to confide in another person.[3] Screening should not be considered a failure if the woman does not wish to disclose.[3] It is important to remain empathetic if this happens and inform the patient to return if they need someone to talk to or to contact a local woman's shelter. It should be made clear to the woman that all cases of abuse are unacceptable and that her health and safety are important. Most women are very vulnerable at the time of disclosure.[3] They can be fearful, embarrassed, or in a state of emotional shock.[3] At this time, many women will be overly compliant with the suggestions; it is not the physician's role to solve the problem for her but rather to support the woman in making decisions.[3] Nevertheless, encourage her to contact the police.[13] Always document that domestic screening was done for reference in the future.[3] It cannot be stressed enough that the physician's response to a disclosure of abuse sets the stage for both the current intervention, and for future interactions with health care providers.[3]

EXAMINATION AND DOCUMENTATION

Proper assessment should begin with taking a history of her presenting complaint and using the patient's own words to describe the injury/illness. She should be asked about other abuse, associated illness such as depression and self-medication/substance abuse. The physician should always ask about suicidal ideation.[3]

A thorough physical examination should be performed with the patient disrobed.[3] The woman who appears to only have a broken arm might not mention the multiple bruises on her back or the bite mark on her shoulder.[14] More importantly, an incomplete exam may miss areas of tenderness that may indicate internal injuries that are not detected on only a cursory exam. [3] A pelvic exam is necessary if sexual assault is suspected.[15] Table 3 provides a listing of signs often present on the physical exam of an abused women. Proper documentation is important. It not only serves as a legal medical document but also guides the user through the steps needed for effective intervention. Suspected domestic abuse should still be recorded in the patient's chart.

A good medical record of domestic abuse would include: the presenting complaint or injuries (including dates, times, and locations of incidents), past injuries and frequency, body map documentation of injuries (type, location, size, color and age), and a description of other health problems that may be related to the abuse.[3] Photographs of the patient's injuries should be arranged after obtaining written consent if possible.[2] Documentation of an assessment of her safety and the development of a safety plan is required once abuse has been diagnosed.[3,15]

THE SAFETY PLAN

A safety plan is composed of strategies which increase the woman's present safety and help her to be prepared in advance for the possibility of future violence.[3] The

physician's role is to inform the patient of her options and respect the decisions that she makes which help her to take control of the situation.[3] It is important to remember that safety intervention should reflect the reality that there are risks attached to every decision abused women make.[3] Finally, make it clear that although you support her decision to return, you do not expect the violence to end.[3]

Assess the threat of violence for the women and her children. Immediate risk can be evaluated by inquiring about access to guns, past use or intimidation with weapons, recent escalation of violence, threats to kill, the presence of substance abuse, extreme jealousy, and whether there has been a separation (or threat of separation), job loss, a pregnancy, or a change in finances recently.[7] The more of these questions that are confirmed, the more immediate risk to the woman. It is necessary to ask about suicidal ideation and whether the woman has considered a plan to kill the abuser.[7] Any time violence has occurred or is strongly suspected, the team must assume that the woman is at risk and assist her in devising a safety plan. The prescription of tranquilizers and pain medication for management of real medical needs must be balanced against maintaining her ability to react to dangerous situations.[3] Finally, never hesitate to arrange immediate admission or delay discharge if it is the only sanctuary available to the victim.[2]

SUPPORT SERVICES IN THE COMMUNITY

It is a physician's duty to go beyond treating the physical injury. He or she must demonstrate greater commitment to aiding victims by knowledge of other professions who may offer psychosocial treatment and other services for the abused woman and other family members.[8] In addition to specialized training in counseling, social workers link women to the resources they need.

An updated list of community services in all practice areas will help provide continuity of care.[3] Small pamphlets or wallet-sized cards that can be easily concealed are helpful.[3] Resources should include: police, hospital services, crisis lines, counseling, shelters, legal and financial aid, immigration assistance, First Nations services, parental relief programs, Crown Attorney's office and family police consultants.[3]

CONCLUSION

Abused women will likely come in contact with a health care professional for the first time in the emergency department. The treatment of a battered woman's medical and/or surgical problems without recognizing that she is being abused and without offering services is simply bad medical care. The more skilled physicians can become at recognizing the pattern of abuse in its early stages, the more opportunity there will be to prevent illness, pregnancy complications, permanently disabling injuries and even death. The utilization of an interdisciplinary team to treat victims of domestic violence increases the detection rate of abuse and significantly improves the care women receive in the emergency department. A busy emergency room physician who remains open, empathetic and has a genuine interest in the women's safety and health will build trust and greatly enhance the possibility of disclosure of abuse. A thorough physical exam, proper documentation, the discussion of a safety plan and referral to community services is the standard of care for abused women. It is the author's belief that maintenance of a high level of suspicion in the emergency room and continued discussion of this once taboo topic will be the key to making a significant difference in these women's lives.

ACKNOWLEDGMENTS

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FEMALE CIRCUMCISION OR GENITAL MUTILATION: A Rational Approach?

By Reena Bhargava and Lubna Tirmizi, MEDS 2000

Note: Certain aspects of the descriptions of the following procedures are directly from informal interviews with several female members of the local Muslim community of London, Ontario (Considering the personal nature of the issue, anonymity was maintained)

INTRODUCTION

Sexuality remains an obscure area, mined with cultural taboos and loaded with anxiety and fear. Thus it is not surprising the subject of genital mutilation provokes emotional reactions both from advocates of it as a justified cultural practice and from the Western world that wants to see the practice outlawed. Female Genital Mutilation is a general term used to describe any sort of physical manipulation performed by a person (whether it be a physician or a midwife) on the genitals of a female. There are four types of manipulations (ritual, "Sunna", clitoridectomy and infibulation) but often female circumcision is used as a collective descriptive term for all four types.[4] The issue of female circumcision is complex and has led to a debate between cultural determinism and health. It is an almost universal belief that changes are needed in the conditions and practice of female circumcision but the extent of these changes is still not determined.

DESCRIPTION AND TYPES OF CIRCUMCISION

Female Circumcision or Female Genital Mutilation can be divided into four basic types, each varying in its degree of genital manipulation.[2,4] The least severe type is called ritualistic circumcision, where the clitoris is merely nicked. This causes bleeding , but little mutilation or long term damage. The second form is simply called circumcision, or "Sunna" by the Muslims. This involves the removal of the clitoral prepuce-the outer layer of skin over the clitoris, sometimes called the "hood"; the glans and body of the clitoris remain intact. Occasionally, the tip of the clitoris itself is removed. Sunna has been equated with male circumcision, because the clitoris itself is generally not damaged. Thus, it is the only type of mutilation which can correctly be called circumcision.

A third, more harsh form of the practice, is called excision or clitoridectomy. This is the most common form and involves the removal of the glans of the clitoris—usually the entire clitoris-and often parts of the labia minora as well.

Finally, the most severe form of the practice is infibulation, or "Pharaonic" circumcision, where virtually all of the external female genitalia are removed. With this type of circumcision, a dramatic excision is performed-removing the entire clitoris and labia minora-and in addition, much or most of the labia majora are then sewn together with acacia tree thorns, and held in place with catgut or sewing thread.[4] The entire area is closed up by this process leaving only a tiny opening, roughly the size of a match stick to allow for the passing of urine and menstrual fluid. The girl's legs then are tied together-ankles, knees, and thighs- and she is immobilized for an extended period, varying from fifteen to forty days, while the wound heals and scar tissue forms.[8]

EPIDEMIOLOGY AND CONDITIONS OF CIRCUMCISION

The World Health Organization (WHO) estimates that 85 to 114 million women across the world have been circumcised and 80 000 procedures are said to be performed in Somalia alone.[1] The countries concerned number more than twenty in Africa, from the Atlantic to the Red Sea, the Indian Ocean and the Eastern Mediterranean.[1] An area of particular interest to international health officials has been the spread of traditional circumcision practices to Europe, Australia, United States and Canada by emigrants. The Centers for Disease Control and Prevention estimated that in 1996 more than 150 000 women and girls in the United States were at risk of genital mutilation.[2]

In most parts of the world, the procedure is performed almost entirely by women; generally local midwives or the elderly in the villages or towns. The age at which girls are circumcised varies both geographically and ethnically. It varies from a few days old (for example, the Jewish Falashas in Ethiopia, the nomads of the Sudan, and some parts of Nigeria), to about seven years old (as in Egypt and many countries of central Africa), to adolescence (among the Ibo of Nigeria).[4] It seems the specific beliefs and practices may vary from country to country. Although not common, the surgery is sometimes performed by medical personnel in health clinics or hospitals. Usually only the affluent members of society can afford having the procedure in such health care facilities.

The instruments used for circumcision range from kitchen knives, old razor blades, broken glass, and sharp stones used in villages, to scalpels used in local health clinics.[4,8] These instruments are rarely sterilized before the operation, and, except in certain urban areas, anaesthesia is almost never used in the process. The incisions are usually made while the girl, often held down by several

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women is lying down on a mat or is in a sitting position. The wounds are frequently treated with herb mixtures, ashes, animal dung or mud to stop the bleeding.[4]

ORIGINS OF THE PRACTICE

Although documentation is difficult to find, it is believed that female circumcision has been practiced for nearly 2500 years- prior to the birth of either Islam or Christianity. The cultural and geographical origins of the practice are unknown. The incidence is, however, so geographically dispersed and occurs among such a variety of cultures that it is reasonable to assume that the practice arose independently among different groups of people.[4] It is interesting that circumcision is commonly assumed to be a part of Islamic beliefs when in fact it existed before the religion of Islam. Islam believes in the circumcision of males as being "Sunna" (blessed) but there is no mention of the circumcision of females in the Qur'an.[7] It seems plausible that Islamic doctrine was interpreted through cultural traditions thus extending the practice of circumcision to women.[7] In the tribal societies female circumcision, as with male circumcision, was initially part of the traditional puberty rites, in which young women and men were introduced into the adult world—a "rite of passage".[2]

Infibulation, the most extreme form of female circumcision, has been traced by some anthropologists and historians to ancient Egypt, hence, the name Pharaonic circumcision.[4] Analysis of Egyptian mummies has shown that women were infibulated during this time, some believe that the practice may have originated there. Others believe that the practice may have existed long before- among herders as protection against rape for young girls who took animals out to pasture, or as a custom among the stone-age people within Equatorial Africa. It may have also been an outgrowth of human sacrificial practices, or the result of early attempts at population control.[4]

JUSTIFICATIONS FOR THE PRACTICE

The reasons and justifications for female circumcision are numerous and complex. As with most traditional practices, the ideological basis lies in the society's cultural, traditional, historical, political, economic and religious background. The commonly given reasons for the persistence of the practice include: sexual control over females, religious requirements, mythical beliefs, and the need to maintain a tradition that has been with these cultures for thousands of years.[4,8]

In contrast to the reasons for male circumcision, one of the most frequently given reasons for female circumcision is the control of the sexuality of females.[8] This is the case especially in areas where the practice is carried out on infants and very young girls, clearly not old enough to be initiated into the adult world. In these cultures, circumcision serves primarily to discourage promiscuity by reducing a woman's sensitivity and desire for sexual intercourse.[8] The primary function of infibulation is to guarantee a bride's virginity. The preservation of virginity is essential for determining a woman's social position in these societies. For a young girl it is a practical choice not to resist being circumcised because she is made to believe that her only role in life is to be a wife and a mother. If she does not find a husband, she may never be able to survive economically or otherwise. Thus if a girl does not undergo circumcision she may believe that her future will be tainted. In the interest of social position, family honor, and economics within some cultures, it is believed that the sexuality of women must be controlled.[8]

The view that circumcision is a valid means of controlling the sexuality of women has been recently questioned. It is suggested that female infibulation is no guarantee of a woman's virginity at the time of marriage: an unmarried woman can have sexual intercourse and then be re-infibulated (also called the "Aladal operation") prior to marriage to disguise the fact from her husband.[5]

A second reason often given as justification for female circumcision has been religion.[4] This response was especially common for males interviewed. The religion that seems to have incorporated the practice most heavily into its culture is Islam.[8] In Africa, the operation is performed by Christians (Catholics, Protestants, and Copts), Muslims, Jews, Animists, and atheists, although the practice does not exist in the teachings of any formal religion.[4]

A third justification is based on the following folk myths: the clitoris represents the male sex organ and if not cut will grow to be the size of the penis; females are sterile until they have been excised, and the operation will actually increase fertility, as well as the number of live births; the operation is a biologically cleansing process that improves the hygienic and/or aesthetic condition of female genitalia. In Sudan, it is believed that a woman is naturally "polluted" and can only be cleansed, and suited for marriage and childbirth, by being excised.[4]

One of the myths helping to perpetuate the practice stems from the "Pharaonic belief in the bisexuality of the Gods". All males and females have both masculine and feminine souls that are represented in their sexual characteristics. The prepuce, or foreskin, of the penis, it is believed, represents the feminine soul in the male, while the clitoris represents the masculine soul in the female. According to the myth, adolescents cannot be admitted into the adult world until they have been rid of the physical characteristics of the opposite sex-hence the justification for both male and female circumcision.[4]

The most widely held justification for the continued practice of female circumcision is the importance of tradition.[8] In a questionnaire given to five rural communities in Nigeria, 280 men and women were asked about their experiences with the practice. In addition, their thoughts as to why the practice continues to exist was queried. The dominant reason given by both men and women was the need to maintain tradition.[4] In some cultures female circumcision can also be accompanied by elaborate ceremonies and joyous celebrations. There may be days of preparation, including cleansing, praying, consuming special food and drink, and performing rituals, such as dancing and singing. The girls are frequently given gifts and are showered with praise and words of support for being brave and becoming women.[8] Although maintaining tradition is often used as justification for the physical manipulation of a young girl's genitals, this point

of view has drawn much opposition from the international community.

MEDICAL COMPLICATIONS

Immediate complications from the female circumcisal procedures can be many and varied. Haemorrhage may occur internally from the pudental and dorsal arteries of the clitoris. There may also be risk of post-operative shock. The resistance of the child may cause cuts in other organs: the urethra, the bladder, the anal sphincter, vaginal walls or Bartholin glands. Also since the instruments used have rarely been sterilized, tetanus (frequently fatal), and septicaemia often result. It is also important to note that the procedures are done without anaesthetics thus are extremely painful for the female involved. The severe pain may cause psychological distress and trauma for especially young girls.[2]

The long-term complications range from infections to maternal mortality. Chronic infections of the vagina and uterus are frequent because the vagina (in the case of infibulation) virtually becomes a semi-sealed organ of the body. A Keloid or dermoid cyst may form on or around the vulva. Other grave complications include dysmenorrhoea, since the menstrual flow cannot escape freely through the minuscule opening. In some cases the menstrual flow may be fully blocked and would require surgical correction.[5]

The most severe result of excision is the development of a neuroma of the dorsal nerve of the clitoris. Vulval abscesses can also develop. Mutilated women can become sterile due to infections which ascend into the reproductive organs.

Further complications during childbirth are unavoidable for infibulated women. Splitting of the scar is always needed to let the baby out. A long labour may result possibly leading to intrauterine foetal death, or birth trauma.[1]

Anonymous reports from local physicians of Muslim origin, emphasize the growing interest in the relationship between the practices of female circumcision and the spread of AIDS. They state that Infibulation has probably become an extra risk factor in the spread of the HIV-virus by predisposition to formation of small mucosal tears during intercourse caused by the abnormal vulval anatomy and through a higher incidence of anal sexual intercourse. It is clear that more data needs to be collected on the role these traditional practice might play in the transmission of the HIV-infection.

FUTURE IMPLICATIONS

An ultimate end to Female Genital Mutilation may not be in the near future but practical steps can be taken to change the current conditions. Basic health education for women and health personnel of the countries where FGM is practiced should be a primary concern for the entire world. If women are aware of increased health risks for themselves and their daughters they may reconsider circumcision. There also needs to be education regarding the risks of the unsanitary operating conditions. At least if the conditions are improved there may be a decrease in some medical complications such as infections. There is concern that banning of female circumcision at the government level will cause an increase in unsafe underground circumcision practices. Hopefully with more information and education, decisions affecting the lives of women will be made by women, and not by cultural beliefs.

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HORMONE REPLACEMENT THERAPY IN THE PREVENTION OF CARDIOVASCULAR DISEASE

By Daniel G. Hackam BSc and J. David Spence BA, MBA, MD, FRCPC, FACP

INTRODUCTION

As recently as 15 years ago, cardiovascular disease was considered a much more important cause of morbidity and mortality in men than in women. Few of the early longitudinal studies on the epidemiology of atherosclerosis even included women; hence for many years, heart disease and stroke was often regarded a disease of middle-aged and elderly men. Today we know that cardiovascular disease is the No. 1 cause of death in women, [1] outranking cancer by a factor of 2 to 1; women also have a worse prognosis than men after myocardial infarction,[2] and following surgery for coronary heart disease (CHD).[3]

Although cardiovascular disease is the leading cause of death in both sexes, women tend to develop the clinical manifestations of atherosclerosis about 10 years later than men. [4] Among younger women, the risk of heart disease is one in nine, and by age 65, the risk climbs to one in three. It has long been thought that this difference in the rate of progression of atherosclerosis between women and men is due to estrogen, an advantage that obviously declines with the onset of menopause. This review focuses on the biological and clinical evidence regarding the role of hormone replacement therapy (HRT) in the prevention of vascular disease, and addresses concerns about the possible effects of estrogen on the risk of breast cancer.

BIOLOGICAL EVIDENCE

The experimental evidence for estrogen's effectiveness as a cardioprotective agent is extensive. The best documented effect is estrogen's action on blood lipoproteins. Estrogen acts in the liver to raise production of HDL cholesterol and reduce circulating levels of LDL cholesterol. Hence less cholesterol is carried to the vascular endothelium and more cholesterol can be transported away. Several authors, however, have calculated that estrogen's effect on blood lipids probably only accounts for 25-50% of its apparent cardioprotectiveness. [5,6]

In 1993, two papers in the Lancet focused on vasodilator effects of estrogen. Rosano et al showed that estrogen acutely improved exercise-induced myocardial ischemia, implicating a vasodilator effect of estrogen. [7] In a subsequent Hypothesis, they suggested that estrogen acts as a calcium channel antagonist, and marshaled arguments that the effect is not mediated by nitric oxide (NO).[8] However, Williams et al showed in surgically postmenopausal monkeys that both long-term estrogen administration[9] and acute estrogen administration prevented paradoxical constriction to acetylcholine, suggesting that the protective effect of estrogen with respect to vasodilation may indeed be mediated by NO. They subsequently showed using N-methyl-L-arginine, that the effects of psychosocial stress on endothelium-mediated vasodilation was mediated by NO.[10]

Nitric oxide is released in areas of high shear, and is not only a vasodilator, but has antiplatelet and other effects which reduce proliferation in the intima.[11] Its counterpart, endothelin, is a hormone released by the endothelium in conditions of low shear, which is not only a vasoconstrictor, but which interacts with other factors to enhance coagulation and vascular proliferation. [12] Spence has hypothesized that nitric oxide and endothelin may be important in remodelling of arteries to conform to flow patterns, with filling in of low shear regions, analogous to meanders in a river.

Recently, Polderman et al reported that women have low endothelin levels, men have high endothelin levels, and that when they undergo sex change surgery and hormonal therapy, their endothelin levels cross over to levels characteristic of their new sex. Juxtaposition of the findings of Polderman et al with those of Rosano et al suggests the possibility that the vasodilator effects of estrogen may be related to antagonism to endothelin.

If estrogen reduces and testosterone increases the pro-atherosclerotic effects of endothelin, then it may be possible not only to confer protection from atherosclerosis on postmenopausal women by estrogen replacement, but also to protect men with androgen antagonists. The challenge, for men at least, will be to find a way of antagonizing testosterone without causing impotence and gynecomastia. It may not be so undesirable to reduce aggression and hostility, which along with atherosclerosis are undesirable accompaniments of masculinization. It is possible that drugs such as finasteride or its analogues, which interfere with 5-alpha reductase, might lead to solutions to this problem.

CLINICAL EVIDENCE

Many observational studies have found a lower risk of CHD in women taking post-menopausal estrogen compared to non-users. Three meta-analyses done early in this decade summarized these findings and reported a 35-50% lower risk of CHD in estrogen users compared to

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nonusers. [13-15] Barrett-Connor and Grady published a more recent meta-analysis based on all studies published through mid-1997.[16] Their summary estimate of the relative risk for CHD among women who ever used estrogen compared to never users was 0.70 (CI, 0.65 to 0.75). By far the predominant HRT regimen in these 25 studies was unopposed equine estrogen.

Does the addition of a progestin, taken to protect women with intact uteruses against endometrial cancer, attenuate the preventive effects of estrogen on cardiovascular mortality? A number of studies have reported the effect of treatment with estrogen plus a progestin, usually medroxyprogesterone acetate, on CHD risk. Using the same statistical methods as above, Barrett-Connor and Grady found a summary relative risk for CHD, based on these studies, of 0.66 (CI, 0.53 to 0.84), highly similar to the estimate for unopposed estrogen therapy. These results, in conjunction with favourable experimental data on the effects of estrogen-progestin treatment, suggest that cardiovascular protection can be maintained with combination therapy.

WHAT ABOUT BREAST CANCER?

The fear of breast cancer is a highly emotional issue, and may be largely responsible for the political stance that can be summarized as follows: "Doctors are medicalizing a normal part of aging and putting all kinds of women on hormones they don't need so that multinational drug companies will make all kinds of money". It is easy for physicians to fall into the trap of dismissing this fear as irrational innumeracy; such attitudes only exacerbate the problem of communication and adversely affect the perceptions of women who are faced with the decision whether to initiate HRT.

It appears that there are three sources of misunderstanding that contribute to a very substantial under-utilization of HRT among women who stand to benefit greatly from it: 1) misperceptions about the age of onset of breast cancer in relation to HRT; 2) a significant overestimate of the incremental risk of breast cancer attributable to HRT; and 3) a significant underestimate of the benefit in proportion to the risk.

Since progesterone replacement markedly reduces, and hysterectomy eliminates the risk of uterine cancer, for most women the main risk of taking HRT is breast cancer. For women age 50 to 70, the cumulative risk of breast cancer is about 4.5% without HRT. The incremental risk attributable to HRT is 0.2% after 5 years of treatment, .6% after 10 years, and 1.2% after 15 years. This means that if a woman starts on HRT at age 60, the risk of breast cancer attributable to HRT, extended out to age 75, would be about 1.5%. The belief that HRT will bring on breast cancer at a young age, similar to that of their young friends, and on which their fear is based, is unfounded.

That risk must be compared with the benefit, for women with vascular disease. It is important therefore to understand how high the risk is, for women that have developed angina, myocardial infarction, or carotid stenosis. As shown above, patients with vascular disease have a very high risk. The benefits of HRT appear to be even greater than those of cholesterol-lowering agents:

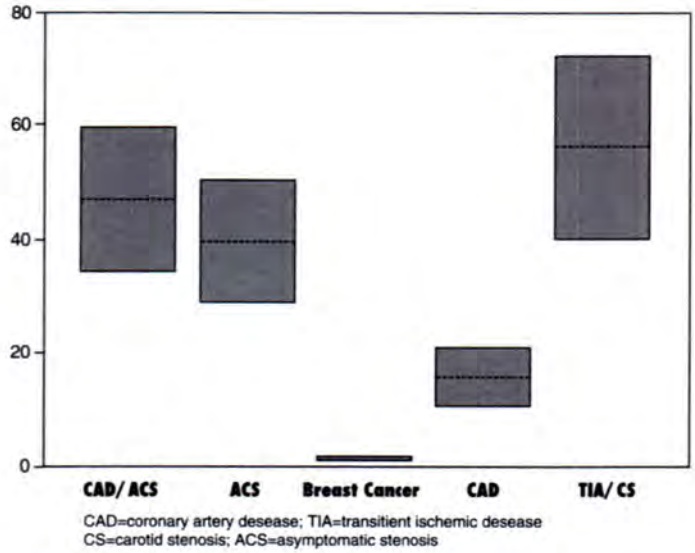

Figure 1. *Six-year risk for women age 50-70 with and without hormone replacement therapy (HRT).* The bars show the 6-year risk of breast cancer versus the risk of death, stroke or myocardial infarction in patients with various vascular conditions: coronary artery disease with asymptomatic carotid stenosis (CAD/ACS), asymptomatic carotid stenosis alone (ACS), Coronary artery disease (CAD) and symptomatic carotid stenosis (TIA/CS), with and without hormone replacement therapy. The top end of the bars for cardiovascular risk is without HRT, the bottom end with HRT; for breast cancer the top of the bar represents risk with HRT, the bottom without HRT. As shown, the increased risk of breast cancer with HRT is very small compared with the reduction of risk with HRT in patients with vascular disease. Reprinted with permission.

HRT reduces vascular disease by approximately 44%, compared to a 40% reduction in coronary events, a 37% reduction in bypass surgery and a 30% reduction in mortality with simvastatin in patients with coronary disease. [17,18] Thus the number needed to treat will be lower than for lipid lowering drugs, and the benefit greater, with HRT. Women with symptomatic carotid stenosis, or a combination of carotid stenosis and coronary disease, have such a high risk that not taking HRT is probably a grave error.

Figure 1 shows the balance of risks and benefits for HRT in relation to various stages of severity of cardiovascular disease, and for breast cancer. The 6-year risk was calculated by extrapolating time in a linear fashion from the published risk of vascular disease as discussed above, and from the risk of breast cancer with and without HRT in the collaborative analysis referred to above. It was assumed that the benefit of HRT was 44%; this is likely a conservative estimate, as women with vascular disease stand to benefit more than the average of the group in which such benefits were observed. [17,18] As shown, the potential benefit of HRT in patients with vascular disease far outweighs the risk.

CONCLUSION

A number of ongoing clinical trials will further clarify the efficacy of HRT in the prevention of cardiovascular disease, as well as shed more light on the risk of breast cancer in HRT users. In the meantime, it seems likely that most post-menopausal women can safely benefit from the

cardioprotective effects of an estrogen–progestin regimen, and those women with risk factors for cardiovascular disease (eg, a strong family history, diabetes mellitus, hypertension, homocyst(e)inemia and so forth) should be strongly encouraged to do so.

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HORMONE REPLACEMENT THERAPY: Issues for Discussion between Physicians and their Patients

By Lynda Newkirk, MEDS 2000

JP is a 55 year old woman who has just undergone menopause. She is generally healthy and presents to her family physician today for a general physical exam and PAP test. Her physician suggests that JP consider hormone replacement therapy. JP is unsure. She states "I have no family history of heart problems so I'm not sure that I need hormone replacement therapy. Besides, I've heard that it increases your chances of breast cancer. Is there something else I could do instead?"

The subject of hormone replacement therapy (HRT) is one of the great debates in medicine today. Who should get HRT? What should they get? When should they start? How long should it be continued? Some physicians think that all post-menopausal women who do not have any absolute contraindications should be given HRT. Is such a blanket statement appropriate? No two women are the same, physiologically or contextually. The pros and cons of HRT must be evaluated for each individual. Physicians must be knowledgeable about the risks and benefits of HRT in order to be able to assist their patient in making an informed personal decision. The purpose of this paper is to highlight some of the key issues that physicians should discuss with their patients who are considering HRT.

THE PROS AND CONS OF HORMONE REPLACEMENT THERAPY

Cardiovascular

The lesser incidence of cardiovascular disease (CVD) in pre-menopausal women in comparison to men of similar age, and the significant increase in CVD in post-menopausal women suggests that estrogen may be cardioprotective. In fact, studies have shown up to a 50% decrease in the risk of cardiovascular mortality in women who take HRT.[1,2,3,4,5] Cardioprotection is potentially the most beneficial effect of HRT, as CVD is the leading killer of post-menopausal women.[5]

It is the estrogen component of combined HRT which is cardioprotective. In fact, it has been suggested that progesterone may oppose the beneficial effects of estrogen. Consequently, in women without a uterus, unopposed estrogen is ideal.[1,3] Women with a uterus require the addition of progesterone to prevent endometrial cancer. One study showed that a hormone regime involving micronized progesterone maintained more of the cardioprotective effects than did a regime involving medroxyprogesterone acetate.[1] Although the cardioprotection may be slightly less than that provided by unopposed estrogen, studies continue to confirm that combined HRT provides significant cardioprotective benefits.[1,3]

Despite the large number of studies which report cardiovascular benefits from HRT, some researchers dispute the beneficial effects of short term therapy.[6] Furthermore, there has been some concern that almost all the studies reported to date have been partially funded by drug companies.[7] Finally, it seems that the cardiovascular benefits of HRT may not be as great for women who have no significant risk factors for cardiovascular disease (i.e. have never smoked cigarettes; do not have high cholesterol levels, high blood pressure, or diabetes; have no parental history of early myocardial infarction; and have a body-mass-index of less than 25).[4] In this population the relative risk of mortality is 0.89, in comparison to the relative risk of 0.51 in the group with at least one cardiovascular risk factor.[4] However, it is likely that the majority of women have at least one of the above listed risk factors. It is important to remember that CVD is the number one killer of postmenopausal women, resulting in six times as many deaths as breast cancer; therefore any degree of cardioprotection is certainly beneficial.[5]

Prevention of CVD is one of the primary benefits of HRT. Therefore HRT should be seriously considered in all women with cardiovascular risk factors.

Bone Health

It is generally accepted that post-menopausal women undergo a period of rapid, estrogen-dependent bone loss. Decreasing bone density predisposes women to osteoporosis and fractures. Osteoporotic fractures are a major cause of morbidity and mortality in Canada today.[8] Studies have shown that HRT inhibits bone resorption and maintains bone density.[2,8,9,10] This significantly reduces the risk of osteoporotic fractures (up to 50% reductions in fracture rates have been reported).[2,8] The favorable effect on bone health is an important benefit of HRT and should be considered in all women, especially those with risk factors for osteoporosis.

Some individuals wonder if calcium supplementation and other conservative treatment strategies such as weight-bearing exercise and vitamin D supplementation are sufficient to prevent accelerated bone loss. It seems

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that while calcium and vitamin D supplementation are beneficial compared to a placebo, they are not as effective as HRT in preventing accelerated bone loss.[8,9,10] Individuals who have decreased bone density or significant risk factors for osteoporosis require more than just exercise and vitamin and mineral supplementation to maintain their bone density. They should seriously consider HRT, or a second line treatment such as bisphosphonates.[9]

Breast Cancer

A major issue of debate has been whether or not HRT increases the risk of developing breast cancer. There have been a number of contradictory findings. The National Cancer Institute of the United States recently carried out a meta-analysis and determined that the use of HRT does increase a woman's risk of developing breast cancer after five years of use.[11] A strong piece of evidence to this regard comes from the Nurses' Health Study,[4,12] a study of 121 700 registered nurses followed between 1976 and 1992. The results of this study find the multivariate adjusted relative risk of breast cancer in individuals taking estrogen supplementation (with or without progestin) to be between 1.28 and 1.41 depending on the hormone regimen.[12] Although this is a relatively small increase in risk, it is significant as the baseline risk that a woman will develop breast cancer at some point in her lifetime is one in eight.[13] It is important to note that the risk of breast cancer seems to increase with duration of treatment. The Nurses' Health Study shows that, for individuals currently using HRT, the relative risk of mortality from all causes in comparison to people who had never used HRT is 0.63, but that it increases to 0.80 after 10 or more years of use.[4] They attribute this to an increase in deaths due to breast cancer. An increased risk of developing breast cancer is the primary drawback of HRT and must be weighed against the cardiovascular, bone health, and other benefits.

Colorectal Cancer Risk

Studies have shown that the use of HRT significantly reduces the risk of colorectal cancers (relative risks reported are 0.54 and 0.71 for colon cancer, and 0.91 for rectal cancer).[14] Since colon cancer is the second most common cancer in women, and the third most common cause of cancer death in the population,[13] this is an important consideration for those evaluating HRT, especially if they have a family history of colon cancer.

Endometrial Cancer

Combined estrogen and progesterone HRT does not increase the risk of developing endometrial cancer.[1,2,15] Studies have shown that unopposed estrogen does increase the risk of endometrial hyperplasia and endometrial cancer in women with an intact uterus, so a combined estrogen plus progesterone approach is mandatory for these individuals who choose HRT.[1,2,15] Physicians should note that when a progesterone cream is used instead of oral/systemic progesterone, blood levels of progesterone may be insufficient to provide a protective effect on the endometrium.[16] These women may effectively be taking unopposed estrogen and must be followed accordingly.

Vaginal Dryness and Urinary Incontinence

Some post-menopausal women report vaginal dryness and urinary incontinence. Studies have shown that oral and/or topical estrogen therapy reduces vaginal dryness and can improve urinary continence.[2,5,16]

Menopausal Symptoms

It has been reported that HRT reduces menopausal symptoms such as hot flushes, insomnia, and night sweats.[5,16]

Neurologic

It has been suggested that estrogen may delay the onset of Alzheimer's disease and may "slow the progression or prevent the cognitive impairment and neuronal degeneration associated with senile dementia and Alzheimer's disease."[14] Further research is necessary before definite conclusions can be drawn.

Weight Gain

Women have expressed concerns regarding weight gain as a possible side effect of HRT. The PEPI Trial demonstrated that women in all treatment groups (including the placebo group) gained weight, and that the only significant difference in a comparison of weight changes was that the women in the placebo group gained more than the women in the unopposed estrogen group (2.1 and 0.7 kg respectively, at 36 months).[1] The reality is that weight gain is a result of consuming more calories than one burns on a daily basis. Women who are concerned about weight gain should be educated about this relationship and counseled on strategies to prevent weight gain, such as regular exercise and a healthy diet.

Bleeding

Sometimes HRT results in bleeding. This is more likely to be a problem if HRT is initiated before the woman stops menstruating. The risk of breakthrough bleeding may be reduced if a withdrawal bleed is brought on by the administration of a progesterone challenge before beginning HRT.[17] Breakthrough bleeding persisting for more than 6 months after the start of treatment or of new onset in someone taking HRT must be investigated by endometrial biopsy.[17] If endometrial biopsy confirms no pathologic cause for the bleeding, the physician may consider changing the hormone regimen. One option is to use a cyclic regimen, whereby the bleeds should be regulated. Otherwise, it may just be a matter of time before the woman stops bleeding.

Other Side Effects

Some other side effects of HRT have been documented, including breast tenderness, headache, and depression.[17] Physicians may need to adjust hormone

doses, types of hormones (i.e. micronized progesterone instead of medroxyprogesterone acetate), or even terminate treatment if a woman is experiencing adverse effects. Women who are considering HRT and are concerned about this issue should be reassured that the treatment regime can be adjusted or terminated if she experiences unacceptable side effects.

In General

The Nurses' Health Study determined that women who are taking HRT have a lower risk of death from all causes than do women who have never taken hormone supplementation (relative risk 0.63, increasing to 0.80 after 10 or more years of use).[4]

COMPLEMENTARY APPROACHES

Women can reduce their risk of developing cardiovascular disease and osteoporosis by adopting a healthy lifestyle. This may be most beneficial when combined with HRT, but is perhaps even more important in women who are unwilling or unable to take HRT. Some elements of a heart and bone-healthy lifestyle are:

- healthy diet (low fat, high fibre, well balanced with food containing sufficient vitamins and minerals)[5,16]
- regular aerobic and weight-bearing exercise[5,16]
- abstinence from smoking[5,16]
- limiting caffeine and alcohol intake[5]
- consider supplements: antioxidant vitamins C and E, calcium and vitamin D (beneficial for bone mineral density) [5,7,16]

The consumption of foods high in phytoestrogens (natural estrogens occurring in plants) may also be beneficial.[5,18,19,20] The best known sources of phytoestrogens are soy products, although they are also found in legumes, wheat, berries, and seeds.[5,18,19] Phytoestrogens are considered to have a mild estrogenic effect, and consequently may reduce menopausal symptoms and be mildly bone and cardio-protective.[5,18,19] A study by Lovati et al. demonstrated that substituting soy protein for animal protein in otherwise identical low lipid diets (20% calories from protein, 26% calories from fat, and a total of 1400 - 2100 kcal daily) significantly reduced total and low density lipoprotein cholesterol in hypercholesterolemic women and men.[20] The effects of phytoestrogens in the diet merit further investigation, but meanwhile, individuals may wish to consider the addition of soy products, or other foods high in phytoestrogens, to their diet. A healthy lifestyle including proper nutrition and exercise is the first step to a healthy body, and consequently physicians should discuss lifestyle issues with all of their patients.

A Natural Approach

Some women are uncomfortable with the idea of taking systemic HRT, and/or only willing to consume natural products. There are strategies for both of these patients. There are topical hormone preparations available for those unwilling to take oral medications, although they will likely not achieve the same systemic effect as oral medications.[16] These women may also benefit from foods which are rich in phytoestrogens.[5,18,19] For those who are looking for a natural approach, many of the available estrogens as well as micronized progesterone are all non-synthetic options.[16]

Alternative Therapies

In recent years society has increasingly turned towards the use of alternative therapies such as naturopathy and homeopathy. A number of alternative remedies have been proposed for the treatment of menopausal symptoms and the prevention of heart disease, osteoporosis, and cancer. There is little scientific evidence to support most of these therapies,[16] and further discussion of these issues is beyond the scope of this paper.

CONCLUSION

HRT is a complex issue. The risks and benefits must be weighed and a decision must be made for each woman individually. A summary of ideas for patient counseling is included as Appendix 1. Currently there is a problem with non-compliance in women who have been prescribed HRT.[16] It is important for women to be involved in the decision making process, to have their questions answered, and to be in agreement with the treatment decisions. An involved, informed patient is more likely to feel positive about and be compliant with HRT. Physicians should discuss HRT and lifestyle issues with all of their perimenopausal patients, helping those women to make educated personal decisions.

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Appendix 1: COUNSELING THE PATIENT

Facts to discuss with your patients:

- HRT relieves many menopausal symptoms.
- HRT is cardioprotective, especially for women who have any cardiovascular risk factors. Cardiovascular disease is the leading killer of postmenopausal women.
- HRT helps maintain bone density, decreasing the risk of developing osteoporosis.
- HRT decreases the risk of developing colorectal cancer.
- HRT does not increase the risk of developing endometrial cancer.
- HRT may cause an increase in the risk of developing breast cancer.
- Some women experience mild side effects while on HRT; some of these may pass with time, but if not modification or termination of treatment is always an option. Consider a three month trial period.

Questions for the woman to ask herself:

- Do I have any cardiovascular risk factors? (smoking, high cholesterol levels, high blood pressure, diabetes, family history of heart disease before age 65, overweight)
- Do I feel that I would benefit from cardiovascular protection provided by HRT?
- Do I have risk factors for osteoporosis? (family history, low bone density, smoker, history of excessive alcohol intake, menopause before age 40, history of menstrual irregularity due to hormone deficiency, long-term use of glucocorticoids, high-dose thyroid replacement therapy, chemotherapy, heparin, primary hyperparathyroidism)[5,17]
- Do I feel that I would benefit from bone density protection provided by HRT?
- Do I have or am I willing to take on a heart and bone-healthy lifestyle? (healthy diet; regular aerobic and weight-bearing exercise; abstinence from smoking; limiting caffeine and alcohol intake)
- Am I experiencing menopausal symptoms? (hot flushes, urinary incontinence, etc.)
- Do I have risk factors for breast cancer? (personal or family history of breast cancer; premalignant breast lesions; early menstruation (<12); late menopause(>52); nulliparity; radiation treatment to the chest; family history of ovarian, uterine, or colon cancer; obesity)16
- How concerned am I about the increase in the risk of breast cancer with HRT?
- Do I have any other questions or concerns regarding HRT and its side effects which I would like to discuss with my physician?

Physicians: For recommendations regarding contraindications, baseline investigations, starting doses, surveillance and trouble-shooting, see "Recommendations for prescribing ovarian hormone therapy" CMAJ 1997; 155(8)1130-1133.

OBSTETRIC FISTULA AND MATERNAL MORBIDITY IN THE DEVELOPING WORLD

By Jennifer Hankins

Obstetric fistula, the vesicovaginal fistula resulting from prolonged obstructed labour, is a condition rarely seen in the developed world today. In contrast, prior to the advent of surgical obstetrical care a hundred years ago, obstetric fistula was very common in women throughout the world. Indeed, it is a condition known to have occurred historically, as demonstrated by the ancient Egyptian mummy of Queen Henhenit of the XIth Dynasty (c. 2050 BC), who appears to have lived with a very large vesicovaginal fistula.[1]

Although obstetric fistula is virtually unheard of in most women in the western world today, for women in the developing world it is as if time has stood still. In Ethiopia alone a hospital has been built for the exclusive care of women with obstetrical fistulas, with 1000 new surgical repairs done each year.[2] The obstetrical fistula rate for women in the developing world is largely unknown, but it is estimated to be high based on high reports of prolonged obstructed labour and maternal mortality. In Africa in particular, death in childbirth is common: the World Health Organization (WHO) estimates the maternal mortality rate in Africa to be at least 640 deaths per 100,000 live births (compared to 8 maternal deaths per 100,000 live births in the USA).[3] Similarly, in Scandinavia, the lifetime risk of a woman dying in childbirth is 1 in 25,000, but in rural Africa the rate may be as high as 1 in 15.[3] The extent of maternal morbidity in the developing world has been difficult to fully appreciate as much of it goes unreported. In general, overall maternal morbidity (including pregnancy-induced hypertension, ectopic pregnancy, postpartum infection, obstructed labour, uterine rupture, uterine prolapse and fistula) in developing countries has traditionally been estimated to be 16 episodes of illness for every maternal death.[4] Given that approximately 500,000 women die every year from complications of pregnancy and childbirth, the extent of maternal morbidity is likely enormous (roughly 8 million women/year). What is significant is that much of this is largely preventable.

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Jennifer Hankins is a fourth year medical student at the University of Western Ontario. Prior to medical school she obtained a BScN from the University of Alberta. Jennifer has an avid interest in international health, having lived in Nepal and India and participated in student projects in Tanzania and Guatemala. This winter she will be going to Uganda for two months to work with the Canadian Network for International Surgery.

The obstetrical fistula differs from the post-surgical vesicovaginal fistula (which results from focal trauma to healthy tissues) in that it is the result of extensive vascular injury and necrosis of pelvic tissues due to prolonged pressure from the fetal presenting part 2. Clearly, additional pathology can also occur during this process. In some parts of Africa, obstructed labour may last for over a week, leading to extensive tissue damage and numerous injuries to multiple organ systems.[2] Thus, as Arrowsmith et al note, "caring for these patients requires much more than simply 'repairing' a vesicovaginal fistula".[2]

In addition to the vesicovaginal fistula, other documented injuries resulting from this "obstructed labour injury complex" include total urethral loss, stress incontinence, hydrouteronephrosis, renal failure, rectovaginal fistula, rectal atresia, anal sphincter incontinence, cervical destruction, amenorrhea, pelvic inflammatory disease, secondary infertility, vaginal stenosis, osteitis pubis, and foot drop.[2] Because of the odor, possible childlessness and inability to carry out daily tasks, the social consequences of these injuries are often as severe: divorce, abandonment by family, worsening poverty, malnutrition, exclusion from religious activities and even suicide may ensue.[2,5] As Harrison observes, "an important feature of obstetric fistula is that it cannot be fully discussed without raising a wide range of social, economic and political issues".[5]

Several environmental factors contributing to the development of obstetric fistula and other associated injuries have been postulated. Firstly, vesicovaginal fistula occur more frequently in young teenage women who marry and become pregnant at an early age.[6] In these women, the pelvis is often not fully developed leading to cephalopelvic disproportion which results in obstructed labour, severe obstetric fistula, rectovaginal fistula and vaginal fibrosis. Poor nutritional states may worsen this phenomenon, as malnourished women are more likely to be of shorter stature and have smaller pelves.[6] In one report from Nigeria, of 174 women with fistulas, 65% were acquired in the first pregnancy, none of the women had had any education (and only 15% of their husbands did), and over 90% married before menarche.[7] Secondly, a lack of utilization of medical resources (i.e., labouring and delivering outside of a hospital setting) also plays a role.[5] Hospitals may be too far away or a woman may not have the resources available to access prenatal care or hospital care at the time of labour and delivery.[5] Additionally, a woman in the developing world may only be able to seek medical care if her husband gives her permission to do so. If he is absent for some reason, she may be forced to labour and deliver at home, even if there is a hospital nearby.[6] Thirdly, traditional practices may also play a role.

In parts of Nigeria, for example, the "gishiri" cut is often practiced in order to treat obstructed labour, infertility, dysparunia, amenorrhea, goitre, backache or dysuria. This involves cutting the anterior and occasionally the posterior aspect of the vagina with a razor blade, and can contribute to obstructed labour and the development of a fistula directly.[2,5,6] Other traditional practices leading to fistula include the insertion of traditional medicines and caustic materials into the vagina to treat such things such as infertility and dysparunia.[6] Lastly, traditional beliefs that evil spirits or wrongdoing cause the manifestations of obstetric fistula impede understanding and knowledge of how to prevent this.[7]

Indeed, understanding and prevention are the keys. Obstetric fistula is more than just a complication of childbirth; in many women it is a chronic, social and physical death sentence that need not exist. If it can be virtually eliminated in the western world, the developing world should be no different. Perhaps most challenging of all is the need for a change in attitude towards women and their health care needs.[8] It has been argued that traditional practices and customs such as early marriage and the use of the "gishiri" cut should be eliminated.[5,6] At the very least, women in the developing world need access to appropriate health care services including prenatal, intrapartum and postpartum care. Universal education about the use and availability of medical services cannot be overemphasized enough. Interdisciplinary cooperation between health care workers and specialists is needed in order that the numerous social and physical complications of obstructed labour are addressed. More information is needed on the extent of maternal morbidity in the developing world. Maternal morbidity and mortality will not decline in the developing world until such action is taken, and until that time, women will continue to suffer needlessly.

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Hypertension
NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.
NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.
Chronic Stable Angina
NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS
NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS
Increased Angina and/or Myocardial Infarction
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.
Outflow Obstruction (Aortic Stenosis)
NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).
Use in Patients with Impaired Hepatic Function
There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).
Beta-blocker Withdrawal
NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS
Use in Patients with Congestive Heart Failure
Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that NORVASC had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.
Hypotension
NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.
Peripheral Edema
Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.
Use in Pregnancy
Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.
Nursing Mothers
It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers.
Use in Children
The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.
Use in Elderly
In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).
Interaction with Grapefruit Juice
Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.
Drug Interactions
As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme.
Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.
Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.
Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.
Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.
Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:
- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin.**
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids
Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.
Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

ADVERSE REACTIONS
NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity.
Hypertension
In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):
Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).
Angina
In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).
The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909): **Cardiovascular:** edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).
NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.
The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia', back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male' and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus', rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, increased sweating. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.
'These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.
The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.
Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms
Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.
Treatment
Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION
Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.
Use in the Elderly or in Patients with Impaired Renal Function
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).
Use in Patients with Impaired Hepatic Function
Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS
Availability
NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE
Store at 15-30°C. Protect from light.

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With desogestrel, the progestin developed by Organon

MARVELON* 21 and MARVELON* 28

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Prescribing Information

Pharmacological Classification: Synthetic steroidal combination oral contraceptive.

Indication: Conception Control.

Contraindications: 1. History of/or actual thrombophlebitis or thromboembolic disorders. 2. History of/or actual cerebrovascular disorders. 3. History of/or actual myocardial infarction or coronary arterial disease. 4. Active liver disease or history of/or actual benign or malignant liver tumours. 5. Known or suspected carcinoma of the breast. 6. Known or suspected estrogen-dependent neoplasia. 7. Undiagnosed abnormal vaginal bleeding. 8. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields. 9. When pregnancy is suspected or diagnosed.

Warnings: 1. **Predisposing Factors for Coronary Artery Disease:** Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use in women who smoke. Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether oral contraceptives accentuate this risk is unclear. In low risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in oral contraceptive-users over 35 years of age. Women should be counselled not to smoke.

2. **Discontinue medication at the earliest manifestation of:**

A. **Thromboembolic and Cardiovascular Disorders** such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis. B. **Conditions which predispose to venous stasis and to vascular thrombosis**, e.g. immobilization after accidents or confinement to bed during long-term illness. Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **PRECAUTIONS.** C. **Visual Defects, Partial or Complete**. D. **Papilledema, or Ophthalmic Vascular Lesions**. E. **Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache**. **Precautions:** 1. **Physical Examination and Follow-up:** Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active. The first follow-up visit should be done three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination. 2. **Pregnancy:** Oral contraceptives should not be taken by pregnant women. However, if conception accidently occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. 3. **Breastfeeding:** In breastfeeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low dose oral contraceptives are harmful to the nursing infant. 4. **Hepatic Function:** Patients who have had jaundice including a history of cholestatic jaundice during pregnancy should be given oral contraceptives with great care and under close observation. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If the jaundice should prove to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported. Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding. 5. **Hypertension:** Patients with essential hypertension whose blood pressure is well-controlled may be given oral contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary. 6. **Migraine and Headache:** The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 7. **Diabetes:** Current low dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives. 8. **Ocular Disease:** Patients who are pregnant or are taking oral contraceptives, may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised. 9. **Breasts:** Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age at first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than 8 years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present. Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression. 10. **Vaginal Bleeding:** Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. 11. **Fibroids:** Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuation of the use of oral contraceptives. 12. **Emotional Disorders:** Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition. 13. **Laboratory Tests:** Results of laboratory tests should be interpreted in the light that the patient is on oral contraceptives. The following laboratory tests are modified. A. **Liver function tests:** Aspartate serum transaminase (AST) - variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated. B. **Coagulation tests:** Minimal elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X. C. **Thyroid function tests:** Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 resin uptake. D. **Lipoproteins:** Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions. E. **Gonadotropins:** LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made. 14. **Tissue Specimens:** Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination. 15. **Return to Fertility:** After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time. 16. **Amenorrhea:** Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy. Amenorrhea, especially if associated with breast secretion, that continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function. 17. **Thromboembolic Complications – Post-surgery:** There is an increased risk of post-surgery thromboembolic complications in oral contraceptive users, after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **MAJOR** elective surgery. Oral contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery. 18. **Drug Interactions:** The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent. Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

Birth control pills do not protect against sexually transmitted diseases (STDs) including HIV/AIDS. For protection against STDs it is advisable to use latex condoms in combination with birth control pills.

Drugs Which May Decrease the Efficacy of Oral Contraceptives:

Anti-convulsants: Carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone. Induction of hepatic microsomal enzymes: Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG. Use higher dose OCs (50 mcg ethinyl estradiol), another drug or another method. **Antibiotics:** Ampicillin, cotrimoxazole, penicillin. Enterohepatic circulation disturbance, intestinal hurry. For short course, use additional method or use another drug. For long course, use another method. Rifampicin. Increased metabolism of progestins. Suspected acceleration of estrogen metabolism. Use another method. Chloramphenicol, metronidazole, neomycin, nitrofurantoin, sulfonamides, tetracyclines. Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation. For short course, use additional method or use another drug. For long course, use another method. Troleandomycin. May retard metabolism of OCs increasing the risk of cholestatic jaundice. For short course, use additional method or use another drug. For long course, use another method. **Antifungal:** Griseofulvin. Stimulation of hepatic metabolism of contraceptive steroids may occur. Use another method. **Sedatives and Hypnotics:** Benzodiazepines, barbiturates, chloralhydrate, glutethimide, meprobamate. Induction of hepatic microsomal enzymes. For short course, use additional method or another drug. For long course use another method or higher dose OCs. **Antacids:** Decreased intestinal absorption of progestins. **Other Drugs:** Phenylbutazone, antihistamines, analgesics, antimigraine preparations, Vitamin E. Reduced OC efficacy has been reported. Remains to be confirmed.

Modification of Other Drug Action by Oral Contraceptives:

Alcohol: Possible increased levels of ethanol or acetaldehyde. Use with caution. **Alpha-II Adrenoreceptor Agents:** Clonidine. Sedation effect increased. Use with caution. **Anti-coagulants:** All. OCs increase clotting factors, decrease efficacy. However OCs may potentiate action in some patients. Use another method. **Anti-convulsants:** All. Fluid retention may increase risk of seizures. Use another method. **Anti-diabetic drugs:** Oral hypoglycemics and insulin. OCs may impair glucose tolerance and increase blood glucose. Use low dose estrogen and progestin OC or another method. Monitor blood glucose. **Anti-hypertensive agents:** Guanethidine and methyldopa. Estrogen component cause sodium retention, progestin has no effect. Use low estrogen OC or use another method. Beta blockers. Increased drug effect (decreased metabolism). Adjust dose of drug if necessary. Monitor cardiovascular status. **Anti-pyretics:** Acetaminophen. Increased renal clearance. Dose of drug may have to be increased. Antipyridine. Impaired metabolism. Decrease dose of drug. ASA. Effects of ASA may be decreased by the short term use of OCs. Patients on chronic ASA therapy may require an increase in ASA dosage. **Aminocaproic Acid:** Theoretically, a hypercoagulable state may occur because OCs augument clotting factors. Avoid concomitant use. **Betamimetic Agents:** Isoproterenol. Estrogen causes decreased response to these drugs. Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity. **Caffeine:** The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine. Use with caution. **Cholesterol Lowering agents:** Clofibrate. OCs may increase the clearance of clofibrate leading to decreased level of clofibrate. Use with caution. **Corticosteroids:** Prednisone. Markedly increased serum levels. Possible need for decrease in dose. **Cyclosporine:** May lead to an increase in cyclosporine levels and hepatotoxicity. Monitor hepatic function. The cyclosporine dose may have to be decreased. **Folic Acid:** OCs have been reported to impair folate metabolism. **Meperedine:** Possible increased analgesia and CNS depression due to decreased metabolism of meperidine. Use combination with caution. **Phenothiazine Tranquilizers:** All phenothiazines, reserpine and similar drugs. Estrogen potentiates the hyperprolactinemia effect of these drugs. Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs use other method. **Sedatives and Hypnotics:** Chlordiazepoxide, Lorazepam, Oxazepam, Diazepam. Increased effect (increased metabolism). Use with caution. **Theophylline:** All. Decreased oxidation, leading to possible toxicity. Use with caution. Monitor theophylline levels. **Tricyclic Antidepressants:** Clomipramine (possibly others). Increased side effects; i.e. depression. Use with caution. **Vitamin B_{12}:** OCs have been reported to reduce serum levels of Vitamin B_{12}.

Adverse Reactions: An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives: • Thrombophlebitis • Pulmonary embolism • Mesenteric thrombosis • Neuro-ocular lesions, e.g., retinal thrombosis • Myocardial infarction • Cerebral thrombosis • Cerebral hemorrhage • Hypertension • Benign hepatic tumours • Gallbladder disease • Congenital anomalies. The following adverse reactions also have been reported in patients receiving oral contraceptives: Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally, as follows: • gastrointestinal symptoms (such as abdominal cramps and bloating) • breakthrough bleeding • spotting • change in menstrual flow • dysmenorrhea • amenorrhea during and after treatment • temporary infertility after discontinuance of treatment • edema • chloasma or melasma which may persist • breast changes: tenderness, enlargement, and secretion • change in weight (increase or decrease) • endocervical hyperplasias • possible diminution in lactation when given immediately post-partum • cholestatic jaundice • migraine • increase in size of uterine leiomyomata • rash (allergic) • mental depression • reduced tolerance to carbohydrates • vaginal candidiasis • premenstrual-like syndrome • intolerance to contact lenses • change in corneal curvature (steepening) • cataracts • optic neuritis • retinal thrombosis • changes in libido • chorea • changes in appetite • cystitis-like syndrome • rhinitis • headache • nervousness • dizziness • hirsutism • loss of scalp hair • erythema multiforme • erythema nodosum • hemorrhagic eruption • vaginitis • porphyria • impaired renal function • Raynaud's phenomenon • auditory disturbances • hemolytic uremic syndrome • pancreatitis.

Treatment of Overdosage or Accidental Ingestion: Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration: • 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then take no pills for one week. • 28-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

Availability of Dosage Forms: MARVELON*21: Each sachet contains a blister dispenser with 21 round white tablets. Each tablet for oral administration contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. MARVELON*28: Each sachet contains a blister dispenser with 21 round white tablets and 7 round green tablets. Each white tablet for oral administration contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each green tablet for oral administration contains inert ingredients. Marvelon is a Schedule F drug.

Stability and Storage Recommendations: Store between 15-30°C.

Product monograph available on request.

References:

1. Marvelon Product Monograph. **2.** Rabe T. et al. *The effects of monophasic and triphasic oral contraceptives on ovarian function and endometrial thickness.* The European Journal of Contraception and Reproductive Health Care. 2 (1997) 39-51. **3.** IMS Health.

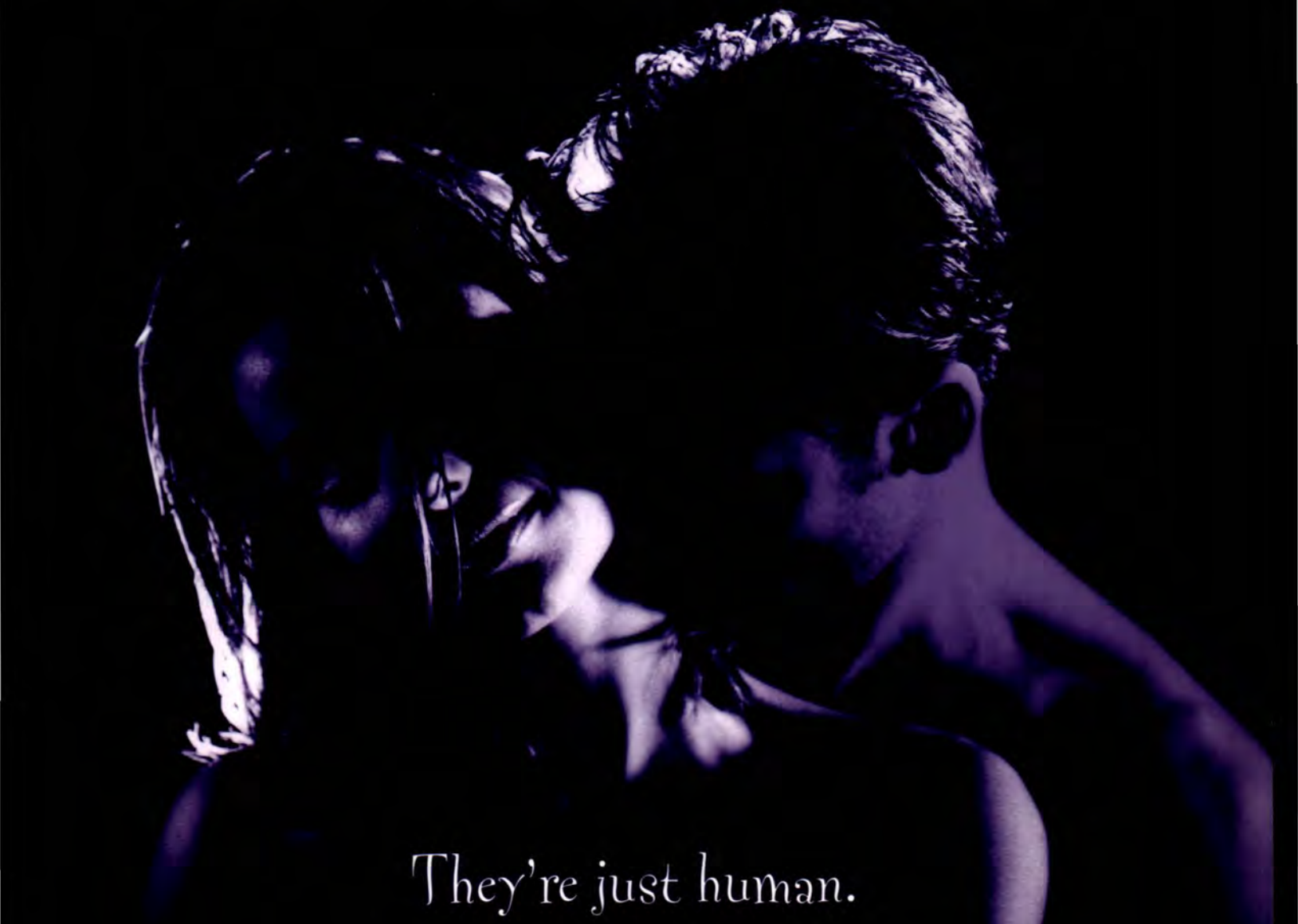
(150 µg desogestrel/30 µg ethinyl estradiol)

℞MARVELON™

With desogestrel, the progestin developed by Organon

PAAB OCPP MEMBER PMAC Organon Canada Ltd./Ltée, Scarborough, Ontario M1H 3E4

Most patients aren't OC non-compliant.



They're just human.

When you recommend Marvelon to your patients, there are a few things you can count on. It's monophasic[1] with a 38 hour half life[2] and a selective progestin[1] to provide excellent ovulation suppression[1,2]. It's one of the world's leading OCs[3]. So while you concentrate on your patients' needs, they can concentrate on more important things.

An OC that accounts for patients occasionally forgetting about their OC.†

†Occasionally refers to either not taking the pill at the same time everyday or missing not more than one pill per month, not more than two months in a row. As with other OC's, if non-compliance exceeds these parameters, patients should consider complementary birth control methods. Please see product monograph for warnings and precautions. For more information, please call 1-800-892-5201

BP CONTROL THAT ENDURES. FROM ONE DAY WELL INTO THE NEXT.

The Pyramids and Sphinx at Giza

℞ Norvasc*
(amlodipine besylate/pfizer)
FOR HYPERTENSION

Long-acting BP control for mild-to-moderate hypertensives

- effectively controls BP at target levels for a full 24 hours and beyond[1,2†]
- intrinsically long half-life maintains plasma levels to reduce BP up to 24 hours after a missed dose[3,4†]
- significantly greater BP reductions during the critical morning hours than nifedipine XL[5§]
- more effective than felodipine at the same dose[6,7¶]

Impressive tolerability after 4 years

- compared with antihypertensives from four different classes, more Norvasc* patients remained on therapy after 4 years[8‡]
- only 3% withdrawal rate among 12,831 patients in 16 clinical studies[9]

† Norvasc* should always be prescribed as once-daily therapy.
§ Both treatments reduced daytime, nighttime and 24-hour mean ambulatory blood pressures. Norvasc* 5-10 mg o.d. versus nifedipine XL 30-60 mg o.d. - 12 week open-crossover in 40 patients, critical morning hours = (0500 to 1100), ($p<0.02$).
¶ Norvasc* 5-10 mg o.d. (n=103) versus felodipine ER 5-10 mg o.d. (n=103) after 8 weeks ($p=0.036$) 82% of Norvasc* patients reached target DBP of ≤90 mmHg versus 69% for felodipine.
‡ Norvasc* (n=114), 83% of Norvasc* patients remained on therapy after 48 months.

Norvasc* is indicated in the treatment of mild-to-moderate essential hypertension when diuretics or beta-blockers are unsuitable. The most common adverse reactions include edema (8.9%) and headache (8.3%).[1]

Consult prescribing information for important safety information and drug interactions.

HERE TODAY. HERE TOMORROW.