

# Spontaneous Abortion

## Introduction

Spontaneous abortion refers to a clinical condition describing the loss of the intrauterine product prior to the viability of the fetus, conventionally accepted as 20 weeks of intrauterine life, or 500 grams of fetal body weight. The term habitual aborter describes a patient who serially miscarries, with three or more miscarriages being taken arbitrarily as the starting point from which a patient is labeled a habitual aborter. The exact frequency of spontaneous abortion in the general population is unknown. With the availability of sensitive beta-human chorionic gonadotropin serum assays, early pregnancies are detected that formerly were written off as simple abnormal prolongations of the menstrual cycle. Five to ten-day delays in the onset of the menstrual bleeding are very frequently diagnosed through the beta subunit as early spontaneous abortions. It is estimated today that more pregnancies are lost spontaneously than are actually carried to term. Therefore, many practitioners believe that it is unnecessary to initiate a full-scale work-up after the first miscarriage. **We would like to emphasize, however, that if an infectious condition precipitates the first spontaneous abortion and is allowed to persist without treatment, the subsequent pregnancies often become high risk and thus jeopardize the outcome of the fetus.** The actual chance that a woman will experience a subsequent pregnancy loss once she has had two spontaneous abortions has changed dramatically during the last 40 years. In the late 1930s, the figure was a staggering 73 percent. By the mid-1970s, this number was reduced to approximately 30 to 35 percent and in our laboratory, since the introduction of aggressive antibiotic therapy, it has fallen to between 5 to 20 percent.

## Etiology of Spontaneous Abortions

### Chromosomal Abnormalities

A chromosomal abnormality is still believed to be the most common etiologic factor behind spontaneous abortions. Indeed, **up to 50 percent of the examined first trimester losses show some kind of chromosomal abnormality.**

It has been speculated that spontaneous, random errors in meiosis or mitosis occur in sperms or in oocytes or during early embryogenesis that will lead to chromosomal damage. An other possibility relies heavily on defects in parental genes that are creating chromosomal breaks in the embryo. The dramatic rise in the number of Down syndrome cases associated with advanced parental age suggests that spontaneous chromosomal damage more common with advancing age. **During the last 10 years, in our patient population, a pregnancy conceived following intravenous antibiotic therapy never had to be terminated due to chromosomal damage. This suggests that bacteria or bacterial toxins are present in the environment in which the early embryogenesis takes place** or in the ovum or in both germ cells. Another possible hypothesis is that a noxious agent **could be inducing the meiotic or mitotic errors.** One particular case comes to mind. A patient of mine whose husband was a carrier of a labile chromosome, a balanced translocation between the terminal bands of the long arm of a No. 3

homologue and the terminal bands of the short arm of a No. 20 homologue. Break points were identified at q27 and p13, respectively. His karyotype revealed 46,XY,t(3;20)(q27;p13). This led to 18 miscarriages in which the miscarried product exhibited identical chromosomal breaks at the same location. I reasoned that an anaerobic bacterial contamination of the uterus, *Peptostreptococcus* could create a less than optimal environment. I recommended intravenous Clindamycin and Gentamycin therapy for both husband and wife. Three subsequent healthy pregnancies delivered on the due date support my notion that intrauterine infections can lead to chromosomal breakage. All the delivered offsprings however are carriers for the unbalanced translocation.

## **Medical Illnesses**

Systemic lupus erythematosus, congenital cardiac disease and renal disease are among the medical diseases associated with spontaneous abortions. The severity of the underlying disease condition determines the outcome of pregnancy. It has been suggested that the high rate of fetal wastage among patients with systemic lupus erythematosus is due to circulating immune complexes. In pregnant patients with congenital cardiovascular diseases, the spontaneous fetal wastage is in excess of 50 percent. With renal disease, especially with coexistent hypertension, the incidence of fetal loss can be extremely high. Individual, uncontrolled studies suggest that diabetes mellitus, especially when there is poor control of the blood glucose level, can lead to increased fetal wastage. Double-blind controlled studies are still unavailable.

The role of the hypoactive thyroid both in infertility and in pregnancy losses is suspected but not proven. I see a frequent association between previous spontaneous abortions and the development of anti-thyroid antibodies leading to hypothyroidism. To me it looks as if the original site for the formation of these antibodies is the uterus with the bad pregnancy. **The developing hypothyroidism is an effect of a previous toxic uterine environment leading to miscarriage rather than the cause of the current miscarriage.**

## **Immunological Factors**

It is believed that women who have repeated spontaneous abortions lack a key serum-blocking antibody that is supposed to protect the fetus from rejection by the mother. The blocking factor belongs to the immunoglobulin G class and acts to protect the fetus from maternal antibodies and subsequent immunological rejection via the coating of fetal antigens on the placenta. It is further believed that homozygosity in the HLA antigen system can prevent the mother from producing blocking antibodies. Desensitization, with a suspension of the husband's white blood cells, is suggested by several centers. Serial injections of intravenous IgG (IVIg) are also recommended. **Immune therapy in dealing with spontaneous abortions disturbs me on several levels. Firstly, patients from my private practice who elected to go through the immunization process did not seem to fare better than patients who elected to have no intervention. Secondly, I cannot ignore the fact that the final product of homogenized white blood cells have innumerable other antigens and that the possibility always exists that immunized women will develop several other unwanted antibodies. Thirdly, when using a series of IgG injections, one should not ignore the fact that they are blood products with all the inherent risks a transfusion. Finally, on a more philosophical level, it is extremely difficult for me to**

**believe that such an intricate system as the reproductive canal, with so many safety mechanisms built in, would go astray without a good reason. In other words, I tend to believe that the sudden emergence of these immunological factors represents a secondary response to an underlying, more profound, process and the suggested “desensitization steps” are addressing the effect or symptom rather than the cause.** In my practice, I abstain from using leukocyte immunization or a series of IgG injections. I advise my patients accordingly. **Recent studies from the scientific literature uniformly discredit the benefit of immune therapy.**

Studies dealing with major **blood group incompatibilities** are contradictory and await further confirmation.

Isolated reports do not show conclusive evidence that **antisperm antibodies** are associated with habitual abortions.

### **Endocrine Factors, Luteal Phase Defect**

Luteal phase refers to the second part of the menstrual cycle that is dominated by the corpus luteum and its main hormone, progesterone. Progesterone is necessary to support an early pregnancy up to eight weeks, when the placenta takes over the progesterone production. Sluggish luteal phase hormone production by the corpus luteum is believed to result in early pregnancy losses. Sub-normally low blood progesterone levels and sonographic measurements of the endometrial echo less than ten millimeters in diameter confirm the diagnosis. On occasion, a poorly developed endometrium can be present despite a normal blood progesterone level.

The incidence of luteal phase deficiency varies, depending on the patient population studied. Among infertile couples, luteal phase deficiency is documented in approximately 20-25 percent of the cases; among habitual aborters, however, it can reach up to 35 percent. **Several years ago, we became aware of sub clinical oophoritis (inflammation of the ovary) as a cause of luteal phase defect.** We have found that correction of the condition with antibiotics can be more rewarding than supporting the luteal phase with progesterone or overdriving the entire menstrual cycle with Clomiphene or follicle-stimulating hormone (Pergonal) during the follicular phase of the cycle. Similarly, bacterial or Trichomonas infection of the endometrium can result in luteal phase defect in the face of completely normal progesterone values. **We resort to progesterone or Clomiphene therapy only if antibiotic therapy fails to restore the endometrium or blood progesterone level in the face of negative endocervical and endometrial biopsy cultures.**

### **Psychological Factors**

It is the consensus of the medical literature that there is no scientific basis for psychogenic factors causing habitual abortion. We share this opinion..

### **Radiation, Drugs, and Environmental Pollutants**

### Radiation

Adequate studies are missing. Serious nuclear accidents could cause radiation induced intrauterine demise. I doubt however a long-term effect on subsequent pregnancies.

### Drugs and Other Substances

These (e.g., cigarette smoking, alcohol abuse and certain psychotropic drugs) have been associated with but not proven to cause spontaneous abortions.

### Environmental Pollution

The cases under study are based on associations and projected causal connections without proper scientific evaluation of the data.

## **Anatomical Causes of Spontaneous Abortion**

Uterine and cervical factors can lead to habitual abortion due to malformation of the Mullerian duct system. A wide variety of congenital defects exist in which there is abnormal fusion of the two ducts. Cases ranging from simple arcuation of the uterine body to complete duplication of the entire uterus and cervix have been seen. The spontaneous abortion usually takes place during the second trimester, when the intrauterine cavity becomes inadequate to support a growing fetus. Surgical techniques are available for enlarging the uterine cavity to accommodate a full-size infant. In general, **anatomical abnormalities account for less than 1 percent of the total number of habitual abortion cases.**

Abnormalities of the cervix due to congenital factors can lead to **incompetent cervix** and typically to second trimester painless dilation followed by spontaneous delivery of a nonviable infant. Surgical procedures are available to correct the condition (Shirodkar or MacDonald).

I, however, **categorically reject the diagnosis of an incompetent cervix in an otherwise anatomically normally formed uterus.** If and when a history of an “incompetent cervix” is diagnosed in a patient with a series of mid-trimester pregnancy losses, we treat the couple for infection, pre and post conceptionally, preferably with intravenous antibiotics. **In our experience, women who experienced habitual abortions and were given the diagnosis of mid-trimester incompetent cervixes have one of the most favorable chances of having normal full term pregnancies following intravenous antibiotic therapy.**

## **Diethylstilbestrol (DES)**

A separate group of uterine abnormalities, associated with diethylstilbestrol exposure during intrauterine life is described and documented through hysterosalpingography. These include a T-shaped uterus with a constricted cavity and cervical and tubal abnormalities. The overall surface area of the uterine lining is reduced when compared with that of a control group. Fortunately, those women whose mothers received DES therapy for habitual abortions are slowly coming to the end of their reproductive years. Still, two observations are worth mentioning here. First, **I found a much wider variety of anaerobic bacteria in the genital culture studies of these women together with Mycoplasma than in women without a DES history.** Secondly, we found that **eliminating suspected abnormal bacterial flora from the genital tract of these**

**women is by far more difficult than in any other groups.** Interestingly enough, identical T-shaped uterine changes were observed in women whose mothers experienced a series of recurring miscarriages without taking DES. I venture the conclusion therefore that the abnormalities associated with DES are not unique to the DES exposure, but rather to an abnormal, bacteria laden maternal uterine environment that is unsuitable for the normal development of the offspring's uterus and unable to hold a full-term pregnancy. **The undisputed beneficial effects of antibiotic therapy in helping DES women to achieve normal, full-term pregnancies makes me conclude that they are most likely miscarrying from the same bacteria that caused the adverse pregnancy outcomes a generation prior. Therefore, at least in part, the DES-associated fertility problems, increased miscarriage rate, higher ectopic pregnancy rate, seem to be caused by a vertically transmitted bacterial flora that originally caused recurrent miscarriages in the mother's uterus.**

### **Uterine Myomata**

Uterine fibroids are either subserosal, intramural or submucosal. Subserosal or intramural fibroids do not endanger intrauterine pregnancy. Submucosal fibroids can lead to repeated losses due to the poor blood supply to the endometrium adjacent to the myoma. We do not routinely recommend myomectomies for habitual aborters unless we can document that the location of the myomata is submucosal. The more patients I see who **conceive and carry perfectly normal pregnancies to term with huge fibroids located in any imaginable part of the uterine body,** the less certain I am as to the exact significance of these tumors in reproduction. At this point, I conclude that **provided every hurdle has been eliminated and there is still no change in fertility outcome, I would consent to fibroid surgery. However, I would refer to the procedure as strictly empirical.**

### **Intrauterine Adhesions**

Intrauterine adhesions can be the result of multiple dilation and curettage. **Ascending infections also play a significant role** in the developing intrauterine adhesions. The condition more frequently leads to infertility than to habitual abortion.

### **Infections**

Implicating infectious agents as the cause of habitual abortions is unfortunately complicated by the lack of properly controlled prospective studies. **We have become convinced during the last 10 years that the single best agent to interrupt a chain of spontaneous abortions is a course of broad-spectrum antibiotics.** Isolated studies in the literature implicate the following bacteria: **Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, Listeria monocytogenes, Salmonella typhosa, Vibrio comma, Plasmodium and Brucella.** The suspected viruses are herpes, cytomegalovirus, variola and varicella. **Candida albicans and Toxoplasma gondii** also have been implicated. From our experience, **we have added Group B Streptococcus, Escherichia coli, Streptococcus faecalis, Coagulase negative staphylococcus, all aerobic bacteria and selective species of anaerobic bacteria to the above list: Actinomyces, Propionibacterium, Clostridium, Fusobacterium, Bacteroides, Acidaminococcus, Streptococcus constellatus and Peptostreptococcus.**

The antibiotics we use cover Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum and a wide range of aerobic and anaerobic bacteria. It is our belief that one miscarriage should be managed with the same seriousness as three or more miscarriages. When the seminal fluid or the endometrial biopsy specimen is found to be positive for any of the above-named bacteria, the pregnancy following a miscarriage without intervening antibiotic therapy has a high chance of becoming a high-risk pregnancy with an unfavorable course, including both maternal and fetal complications. **Antibiotics given after the first miscarriage for isolates we believed could be the cause yielded healthier subsequent pregnancies with much more favorable fetal outcomes.** In our laboratory, the work-up of the habitual aborter is initiated with a meticulous bacterial screening of the male's seminal fluid and the female's endometrial biopsy specimen. No further test is proposed or administered until the implicated bacteria are eradicated with single or multiple antibiotic courses. Our experience shows that the genital flora is one of the most stubborn to be influenced with oral antibiotics therefore lengthy courses of broad-spectrum antibiotics are often necessary.

## Treatment for Habitual Abortion

Since, in our experience, bacterial infections are by far the most important cause of spontaneous abortions, it is crucial to utilize antibiotic therapy as the backbone of management.

Previous studies from this laboratory using oral antibiotic therapy have convincingly shown that **pregnancies, conceived without intervening antibiotic therapy following primary or multiple miscarriages, were far less likely to go to a term delivery or to yield delivery of healthy newborns, when compared to those pregnancies where the patient was sufficiently treated with antibiotics.** These results were duplicated in recent years using intravenous broad-spectrum antibiotics and short summaries of both articles will be provided at the end of this chapter.

The selection of the antibiotics is based on microbiological testing of genital-tract secretions. Samples are taken from the seminal fluid, the cervical and vaginal secretions, and from the endometrial biopsy. It is obvious, therefore that any infertility laboratory cannot function without using the expertise of a well qualified, dedicated microbiological laboratory. Most of the bacterial infections that cause miscarriages are asymptomatic and could have been present in the genital canal for decades. **The bacteria, in large part anaerobes, exhibit a slow growth rate and require long incubation periods. Commercial laboratories providing negative reports within 48 hours, or signing out laboratory slips with "normal flora", "no growth" are doing the greatest disservice to the infertility population.** Unfortunately, 10-day incubation periods for high-volume centers are impossible. It is of utmost importance that the laboratory has its interest invested in infertility workups. In lieu of doing detailed culture studies recently more and more practitioners randomly select broad-spectrum antibiotic combinations that can hurt more than benefit. This type of therapy is a hit and miss venture. Certainly, pregnancies will occur if the guessing was correct. However, in those who have received the wrong antibiotics, either resistant strains will develop or a false sense of security will take over that the infection has been taken care of.

Our antibiotic therapy is based on test results provided by our laboratory. We are state licensed and participate in routine proficiency testing. For any suspicious organism, a sensitivity report for specific antibiotics is given. We use a wide selection of both oral and intravenously administered antibiotics. Looking back at the past twenty-five years as an infertility specialist, I can state without hesitation that **antibiotic therapy alone when compared to any other remedy available for infertility, including assisted reproduction, has yielded more pregnancies, healthier newborns and, in the case of habitual aborters, was by far the best remedy to prevent another miscarriage.**

## **Therapy with oral antibiotics**

Ideally, if possible, we try to select oral antibiotics first. Experience shows that in order to change the asymptomatic bacterial flora the therapy courses have to be longer and have to include multiple broad-spectrum antibiotics, following one after the other. Our most commonly used antibiotics include Doxycycline, Erythromycin, Augmentin, Zithromax, Flagyl and Keflex. Based on sensitivity reports, the antibiotic is selected and full therapeutic doses are given, calculated for body weight for two to three weeks for each antibiotic. The combination of two broad-spectrum antibiotics can mean a five to six week therapy regimen. As routine, following the completion of the entire therapy course, a two to three week waiting period is requested, when repeat culture studies are performed. Since it will then take another two and a half to three weeks before reporting the follow up culture, if additional oral therapy is needed, it is possible for the couple to spend the first few months of their infertility work up just going through antibiotic therapy.

Once the last culture study shows satisfactory results, the couple is allowed to try spontaneously to achieve their next pregnancy. For us, the event of any pregnancy is the best proof for tubal patency; thus, we feel HSG is not indicated. Similarly, hormonal abnormalities correct themselves following antibiotic therapy; at this point we don't order hormonal work up either. If the age of the wife is under 35, we will allow at least a six-month trial before initiating any other fertility test, procedure or treatment regimen.

If resistant bacteria are still isolated in follow-up cultures, we follow several treatment schedules. If intravenous antibiotic therapy is not an option, our first choice is **cyclical antibiotic therapy**, from Day-1 through Day-14 of the menstrual cycle or to the day of the ovulation. Both husband and wife are on antibiotic therapy according to the sensitivity report. If and when pregnancy does occur, we elect post-conceptual therapy for the wife alone with safe antibiotics. The oral postconceptional therapy is given for a two to three week duration.

## **Intravenous Antibiotic Therapy**

Special situations for intravenous antibiotic therapy

### 1) Failed Oral Therapy Regimen

If the time, inconvenience and expense associated with intravenous therapy are acceptable, following a failed oral therapy regimen, we offer intravenous ambulatory

broad-spectrum antibiotic therapy for the couple. We administer a number of antibiotics through our center, again, following sensitivity reports on the bacteria. **The therapy, typically given for a ten-day duration, uses midline catheters with a portable pump system that allows the patient to return to work and function fully.** With moderate limitation of physical activity, basically most job related activities could be performed.

2) Advanced Age

When a female patient is at or above forty, we recommend intravenous therapy. Since time is at a premium in this age group, intravenous therapy will achieve maximum benefit in the shortest period of time.

3) Unduly Long Infertility History

When a couple has gone through a number of previous procedures resulting in miscarriages, intravenous antibiotics will be recommended. Most of these patients are emotionally exhausted and there is no room for error in under treatment.

4) Previous IVF Cycles

Often a couple may present with history of a series of failed IVF cycles, when an embryo implanted but a miscarriage followed. Again, it is our experience that intrauterine infections will force the healthiest embryos to miscarry. IVF has a very limited role in the management of habitual abortions. Later in this chapter I will return to this issue.

5) Previous failed IVF cycle with ICSI

Previous failed IVF cycles, when ICSI was needed for poor semen quality or poor fertilization. In our experience, in a number of couples where a previous ICSI procedure was needed, a perfectly normal fertilization was achieved following intravenous antibiotic therapy.

6) Active management of pregnancy.

Following the DES and Thalidomide disasters, the obstetrical profession retreated behind defensive lines. For almost two decades there was a reluctance to offer any kind of drugs to pregnant patients. I agree with this conservative approach except for the administration of antibiotics. **We use oral or intravenous antibiotics routinely and liberally during the course of a pregnancy and we start with aggressive postconceptional antibiotic therapy in habitual aborters directly after the first blood pregnancy test turns positive; that is, 10 to 12 days after conception.** The antibiotics are administered in full therapeutic doses for two to three weeks orally, or at least ten days intravenously.

We evaluate patients all through pregnancy with repeated cervical cultures. **We recommend repeating the IV antibiotic therapy if and when premature labor develops or just prior to delivery, when and if an unduly high colony count of**

**certain bacteria is recovered from the vaginal canal in order to prevent neonatal infections.** As I mentioned before, we do not use the terminology “bacterial vaginosis”, which in our opinion reflects ignorance, rather we use the full benefit of our laboratory to assess the complete bacterial profile of the vagina and cervix.

7.) Incompetent cervix

A much-debated obstetrical condition is the incompetent cervix. I categorically reject the existence of this condition as a disease entity. Unless there is a documented congenital defect in the cervical musculature, based on experience gained following the use of broad-spectrum intravenous antibiotics, **I firmly believe that the incompetent cervix represents an infected uterine environment that is about to expel the product.** For us, the history of incompetent cervix is a favorable predictor for exceptionally good results with broad-spectrum intravenous antibiotic therapy. Quite often we see aerobic bacterial overgrowth in these patients. My office often sees patients who were given cerclage at an other center and intravenous antibiotics by us. Despite the fact that the cerclage is removed around the 37<sup>th</sup> completed week of pregnancy labor does not begin until the due date. In general, we advise against repeated cerclage. We prefer repeating an intravenous antibiotic therapy midway through the pregnancy if the cervix starts opening.

**Other Treatment Available for Habitual Abortions.**

Fertility drugs

The rationale behind giving Clomiphene, Pergonal or other injectable fertility drugs following several miscarriages is the idea that by stimulating a system that does not want to hold onto a pregnancy, we are creating a better-nourished uterine lining, which is more suitable for implantation of an embryo. Following Clomiphene therapy, both Estrogen and Progesterone levels tend to rise, and the cycle functions in an overdrive. With injectable fertility drugs, the stimulation is multiplied several fold. By implanting twins or triplets into the uterine cavity, the argument goes, even if local hostile factors eliminate one or two, one embryo will go full term. I have trouble with this rationale. Unless we prove the uterine cavity free of harmful bacteria, the surviving embryo will be exposed to those bacteria.

In a few cases, when careful bacteria studies documented a germ-free uterine environment and triplets were conceived following an IVF procedure, I witnessed the miscarriage of one or two of these conceptions while the third managed to survive. Was there an antibody or some other embryo toxic material that was absorbed by sacrificing two embryos, thus allowing the third embryo to go to term? On similar ground, when antibiotic therapy is still followed up with miscarriage, **in the face of repeatedly negative endometrial cultures, I still consent to an IVF procedure hoping that by implanting multiple embryos, the adverse condition can be overcome.** I have to emphasize, however, that this situation, in my judgment, should be very rare and should be one of the last resorts to cope with habitual abortions.

### Aspirin or Mini-Heparin

The first histological phenomenon within the placenta of a miscarried product is hyaline fibrinogen blood clots within the small blood vessels. Either Heparin or aspirin tend to delay blood clotting, thus making it more difficult for these blood clots to form. The scientific argument behind giving mini doses of Heparin or baby aspirin daily to a patient with a history of repeated miscarriages is the assumption that these blood clots are the primary cause of the miscarriage. Obviously, administration of these two substances assumes a permanent condition that in our experience readily changes after antibiotic therapy.

I, for one, do not use either aspirin or Heparin, but when the question is posed would I object if the patient takes it upon herself to administer both Heparin and aspirin for several weeks during the early part of the pregnancy, I have no objections, since, to my understanding, neither of these drugs have harmful fetal side-effects.

### Luteal Phase Progesterone Support

I have difficulty believing that in the face of normal luteal phase progesterone levels, measured at two to three day intervals, added Progesterone vaginally, orally or in injection form, would make any difference. Even if during the luteal phase, the Progesterone level drops, **I believe a bad pregnancy is reflected in a dropping Progesterone level and added Progesterone would not improve the quality of that pregnancy.** The picture is, of course, totally different in a Pergonal-stimulated cycle or in every IVF cycle when injected fertility drugs are used. The over stimulated ovaries, especially if they are repeatedly traumatized by follicular aspirations, tend to develop luteal phase defects due to the nature of stimulation itself. In these situations, luteal phase support with progesterone is in order.

### **Corticosteroids**

During the years, a number of antibodies have been discovered in the blood of women with habitual abortions. These findings gave rise to the general belief that these antibodies may be the cause of the miscarriages. Thus, in the mid-70s, high doses of Medrol, a steroid was used for immune-suppression therapy. This practice was completely abandoned, however, when the first aseptic bone necrosis developed. Today, the vestiges of Medrol and other steroid therapy still lingers on in much smaller doses given for a few days either prior to or directly after ovulation or all through the luteal phase. The small dose, however, makes one wonder about any therapeutic effect of this remedy. **There is no publication in the scientific literature supporting steroid therapy. I do not prescribe steroids for habitual abortions. I give Medrol during an IVF cycle because most IVF centers use it. I clearly explain to the patient however that in the dose I am giving it, there is no proven benefit to it.**

### Cerclage, Repair of Uterine Septum, Resection of Submucous Fibroids, Intrauterine Adhesions.

As mentioned above, I categorically reject the existence of a condition referred to as incompetent cervix. **The condition represents a contaminated uterus trying to deliver a fetus following painless dilation of the cervix.** Performing cerclage represents either admission of our inability to identify these organisms or total ignorance of nature's way of eliminating an infected pregnancy. At the present time, my attitude is the same towards cerclage as towards aspirin therapy. If proper antibiotic therapy has been administered, provided skillful hands perform the procedure, it probably does not damage a pregnancy. **The obstetric community stubbornly adheres to this entity. Patients are often frightened and cajoled into surgery.** I allow my patients to proceed with it, but the fact that my treated patients do not go into labor following the removal of the cerclage at 37 weeks tells the story: the intrauterine conditions have been restored to normal.

I have difficulty also proposing the removal of a septum; sub-septum or correction of arcuate uteri attributing the cause of miscarriage to implantation on an unfavorable area of the uterus. Anecdotally, I have heard cases where pregnancies went to term after septum resection. Careful examination however revealed that following the septum resection, the patient was given several days of broad-spectrum antibiotic therapy intravenously.

Similarly, resecting submucosal fibroids, eliminating adhesions or removing intrauterine polypi, procedures performed all too often have no solid scientific support. Whether any of these procedures have any beneficial effect, is still to be seen. I find D&Cs and hysteroscopies during an infertility workup to be the two most abused procedures.

### Vitamins, Nutrients and Other Dietary Changes

There is no proof in my practice or in the literature that any vitamin supplement, or any dietary change or health food supplements would prevent habitual abortion.

## **Clinical Experience**

A twelve year experience from our laboratory using oral antibiotic therapy in the treatment of habitual abortion was summarized and published in 1986; **Outcome of Subsequent Pregnancies Following Antibiotic Therapy After Primary or Multiple Spontaneous Abortions.** In SURGERY, Gynecology & Obstetrics, Vol.163, 243-250.

This retrospective study compared the pregnancy rate, the courses of pregnancy, the perinatal maternal and fetal morbidity and the outcome of the newborns in those patients to whom antibiotics were administered after primary or multiple spontaneous abortions with a group who did not receive antibiotics prior to the conception of the next pregnancy.

Couples involved in the study were drawn from the patient material of The MacLeod Laboratory for Infertility.

Between January 1979 and July 1981, the medical team at The MacLeod Laboratory has consulted or directly treated 306 infertile couples from the greater metropolitan area in which the wife had experienced one or more prior miscarriages. The seminal fluid of the husband was routinely cultured for Mycoplasma, Chlamydia trachomatis and aerobic and anaerobic organisms. All of the couples were advised to begin a four-week therapy course of Vibramycin (Doxycycline). If cultures were positive for Mycoplasma or for aerobic and anaerobic organisms after the four-week Doxycycline therapy course, additional antibiotics were ordered according to the sensitivity report.

Of the 100 couples who elected to take antibiotics, 96 used 100 milligrams twice daily of Doxycycline for four weeks and four used 500 milligrams four times one daily of Tetracycline for four weeks. In addition, 49 used 500 milligrams four times one daily for two weeks, four patients took 500 milligrams four times one daily of Erythromycin for two weeks and four patients received other non-Tetracycline type antibiotics, such as Ampicillin or Keflex (cephalexin). Sixty-one per cent of the couples who accepted the recommended antibiotic treatment regimen received two or more different types of drugs with the maximum length of total antibiotic therapy for 12 weeks. All of the antibiotics were ordered for both husband and wife, and when they were ordered for specific bacteria treatment, a follow-up culture was requested approximately two or three weeks after the conclusion of the course of therapy.

Of the 306 couples who were referred to us during this period, detailed follow-up studies, including direct telephone conversations with the patients and referring physicians, were available for 254 (83 percent) of these women, after excluding those couples who reported that they had stopped trying for a pregnancy after divorce or separation had occurred. For this reason, only those patients who took more than two weeks of antibiotics were considered to be adequately treated.

Among the 100 couples who accepted the antibiotic therapy, bacteria were isolated from the seminal fluid of the husband. These were: Mycoplasma only, 29; aerobic and anaerobic bacteria only, 9; Chlamydia trachomatis only, 13; Mycoplasma and aerobic and anaerobic bacteria, 8; Mycoplasma and Chlamydia, 12, aerobic and anaerobic bacteria and Chlamydia, 5, Mycoplasma, aerobic and anaerobic bacteria and Chlamydia, 8, and no isolates, 16. For those with aerobic and anaerobic bacteria, additional antibiotic therapy was prescribed. These were Peptococcus species, 12 couples; Group B Streptococcus, 4 couples; Bacteroides species, three couples; Fusobacterium, two couples; Veillonella, two couples; Klebsiella, one couple and Escherichia coli, one couple. The most common reason for Erythromycin therapy was a Tetracycline-resistant Mycoplasma infection (27 couples).

## **Results**

### **Fertility Outcome**

Couples who used antibiotics were more likely to achieve a pregnancy (70 percent) than those who did not (66 percent) ( $p < 0.03$ ). Of the 254 women observed, 180 eventually became pregnant. One hundred and thirty-seven (76 percent) delivered a viable infant. Antibiotic users

had a reduced likelihood of subsequent abortion (10 versus 38 percent) ( $p < 0.01$ ). Of the 43 women who aborted, the trimester of abortion was unrelated to the use of the antibiotics. When examining length of antibiotic therapy and chance to abort the following pregnancy, there was a significant correlation ( $p < 0.001$ ) between length of antibiotic therapy and reduced number of subsequent abortions.

### **Maternal and Fetal Complications**

The incidence of premature rupture of membranes and postpartum fever was significantly less frequent in the treated group, three (4 percent) versus 30 (46 percent) and three (4 percent) versus 23 (35 percent) respectively.

In the untreated group, there was a significantly lower percentage of normal vaginal delivery (56 versus 69 percent) ( $p < 0.01$ ). When cesarean section was indicated, however, **in the untreated group, a significantly higher percentage was indicated for fetal reasons** while the majority of patients in the antibiotic treated group were cesarean sections for maternal reasons. The incidence rates of meconium during labor and fetal distress developing during the labor process were significantly lower among those women who were treated with antibiotics prior to conception.

In examining **neonatal fetal complications**, there was a significantly higher occurrence of respiratory distress syndrome, infection and hyperbilirubinemia among those infants who were born to mothers without antibiotic therapy (Table I).

When comparing the Apgar scores, those patients who received antibiotics tended to deliver babies with seven or more one minute Apgar scores, while there was a wide spread of Apgar scores assigned to babies who were born to mothers who had not received antibiotic therapy. There was a significant dose response relationship between the length of antibiotic therapy in weeks and the one-minute Apgar score. None of the babies whose mothers received antibiotics for six weeks or more had less than a 9 one-minute Apgar score while only 80 percent of the babies delivered by mothers without antibiotic therapy had a 7 or more one minute Apgar score

The mean weight of infants delivered to mothers without antibiotics was 3,090 grams, significantly contrasting the mean body weight of 3,529 grams of infants who were born to mothers with antibiotic therapy ( $p < 0.001$ ). The time of delivery was also significantly affected by the administration of antibiotics. **Those who did not receive antibiotic therapy had more often premature deliveries.**

Similar significant differences were observed in the frequency of meconium (zero versus 15 percent), and fetal distress (6 versus 26 percent) ( $p < 0.03$  and  $p < 0.04$ ).

### **Logistic Regression Analysis**

Of the 137 patients who delivered a viable infant, the use of antibiotics was associated with a decreased risk of meconium ( $p < 0.007$ ), fetal distress ( $p < 0.001$ ), premature rupture of membranes ( $p < 0.001$ ), postpartum fever ( $p < 0.001$ ), respiratory distress syndrome ( $p < 0.009$ ),

hyperbilirubinemia ( $p < 0.004$ ), birth weight below 3,000 grams ( $p < 0.001$ ) and deviation from the ideal delivery date of 280 days ( $p < 0.001$ ). Fetal distress, hyperbilirubinemia and deviation from the ideal gestational age were also significantly associated with increased number of years trying to become pregnant ( $p < 0.03$ ,  $0.004$  and  $0.05$ , respectively). Also, patients in whom the recommendation for antibiotic therapy was based upon empirical grounds had a lower risk of hyperbilirubinemia ( $p < 0.04$ ). The odds of having these complications ranged from 5.0 to 18.7 times higher for nonusers of antibiotics as compared with users.