

## Review

Immunization of pregnant women: reproductive,  
medical and societal risks

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## Abstract

Establishing successful vaccine programs for pregnant women would be the quintessence of preventive medicine when you realize the preventive potential for reproductive problems of many of the new and old vaccines. The development of vaccines to prevent maternal, fetal and newborn disease is actually in its infancy. The risks and benefits are discussed in detail as well as the most appropriate and inappropriate time to immunize women of reproductive age and pregnant women. The great majority of risks are theoretical, but the problem is that birth defects and other developmental and reproductive problems are in the group of “diseases of affliction” which means that there are tremendous emotional upheavals in families affected with serious reproductive problems. The failures in reproduction are so common that immunization of a pregnant women has potential deleterious consequences. A consortium of government, academia and industry must work together and an appeal to the more responsible members of the law profession to solve the problem of non-meritorious litigation has been in place before manufacturers of vaccines will be willing to initiate the development of new vaccines. The potential for reducing the incidence of birth defects, prematurity and neonatal infectious disease exists, but it will be difficult to initiate these programs because vaccine makers may be unwilling to assume an additional burden of negligence litigation. Certainly, it is clear that we could provide a safe vaccine for Group B streptococcus and infant botulism that would be of immediate benefit and the potential for reducing other diseases is realistic. This is not going to be an easy task.

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## 1. Introduction

The medical, social and legal risks of immunizing pregnant women against infectious agents for their protection, as well as their infant's protection is an important issue. Emphasis has been placed on maternal immunization primarily for protecting newborns and infants. But there are many other reasons for developing or utilizing vaccines before or during pregnancy, beyond the protection of the newborn. Besides the usual reasons for utilizing immunizations to protect the mother and the neonate, the threat of bio-terrorism adds a new dimension to the necessity for addressing this issue.

The potential advantages for thinking about vaccinating pregnant women include an array of possible programs associated with risks and benefits.

The immunization of pregnant women: purposes and issues of safety.

1. Preparation of vaccines against infectious agents that are known to result in reproductive pathology and congenital malformation if the infection of the mother occurs during pregnancy.
2. Vaccines used routinely to protect the population, but may be administered during pregnancy, i.e. influenza, tetanus and other vaccines. Should these and other routinely used vaccines be administered to women during pregnancy if they are medically indicated?
3. Vaccines to protect women from diseases to which they are susceptible because of pregnancy (poliomyelitis, hepatitis).
4. Vaccines for use before or during pregnancy, primarily to protect the newborn and infant via maternal transplacental antibodies, i.e. group B streptococcus (GBS).
5. Prevention of intrauterine infection that has been alleged to initiate premature labor.
6. Preparation of a vaccine for use before or during pregnancy to protect both the mother and the neonate, i.e. botulism toxin vaccine.

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## 2. The potential or hypothetical risks of immunizing pregnant women just before becoming pregnant or during pregnancy

1. Transmission of an attenuated virus to the placenta or fetus [1–9].
2. The very remote risk that the vaccine would result in reproductive effects, congenital malformations, abortion, growth retardation, stillbirth, and an array of neurological effects [10].
3. Idiosyncratic or toxic reactions to the mother or prospective mother.
4. Ineffectiveness of the vaccine.

## 3. Organisms that infect the fetus, placenta or neonate

There are several groups of infectious organisms that have real or potential for affecting the pregnant woman, her fetus, or neonate.

1. *Congenital embryo or placental infection*: herpes simplex, CMV, toxoplasmosis, rubella, syphilis, HIV, coxsackieviruses, parovirus B-19, hepatitis B, malaria, Venezuelan equine encephalitis, varicella.
2. *Neonatal infections*: GBS, *Hemophilus influenzae* type B, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*.
3. *Prematurity*: *Bacteroides*, *Fusobacterium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Capnocytophaga*, *Clostridium*, *Leptospira*, *Trichomonas vaginalis* (bacterial vaginosis).
4. *Nursery epidemics*: *Klebsiella pneumoniae*, *Flavobacterium meningosepticum*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Citrobacter diversus*, *Enterobacter* and *Salmonella* species.

Besides determining which vaccines have to be developed and which available vaccines should be utilized, it also has to be determined at what stage of pregnancy the vaccine should be administered. Besides these logistical problems of timing, efficacy and safety that are related to all immunization procedures, new problems arise because of the fact that the mother is pregnant. The marked differences in the sensitivity of developing humans to environmental toxicants, drugs and physical agents is best exemplified by comparing adult sensitivity with the sensitivity of the embryo and fetus. During early embryonic development (organogenesis) as well as, early and late fetal development, the embryo manifests toxic effects to some, but not all, environmental toxicants, at lower exposures than result in deleterious effects in the adult. This is due to the fact that all the organs in the adult have formed and reached full-size. Agents that interfere with embryonic development can result in congenital malformations, growth retardation and permanent reduction in the optimal number of cells in vital organs, i.e. the brain and reproduc-

tive organs. In the past 50 years we have learned a great deal about agents which have the potential for reproductive toxicity and teratogenicity. A half-century ago, Gregg had described the teratogenicity of rubella virus infection during pregnancy [11]. The teratogenic risk of the folic acid antagonists (aminopterin) was established [12,13] and there were experimental studies indicating that nutritional deficiencies could produce birth defects in animals [14]. As of 2002, there are over 50 teratogenic agents or reproductive toxicants that have been established as harmful to the developing human embryo and fetus at exposures that are attainable from drugs, chemicals and physical agents [15–19]. There are many other environmental toxicants that have been demonstrated to be harmful to developing non-human mammalian embryos at high exposures, but the exposures to the human embryo either do not occur or occur at such low levels, that the embryo and fetus are not affected.

We know very little about the reproductive effects of vaccines, because they are infrequently given to pregnant women. But there is a significant amount of data about the pregnancy risks of rubella vaccine and there are apparently minimal reproductive risks associated with inadvertent administration of rubella vaccine during the first trimester [1,3,7,8,20].

When one enters a new frontier by administering new pharmacological agents to pregnant women, i.e. vaccines that have been newly developed or have never been administered to pregnant women, it is important to recognize that new problems that may arise.

## 4. Problems

**Problem #1.** The first major problem is the emotional stigma associated with reproductive failures along with other disease that historically carry an emotional burden.

The problem of any type of reproductive failure is interpreted by many families as a punishment that engenders guilt and anger. The anger can be self-directed in the form of depression or can be directed toward health care professionals. The diseases of affliction include many diseases that relate directly or indirectly to reproduction. Reproductive problems encompass a multiplicity of diseases including sterility, infertility, abortion (miscarriage), stillbirth, congenital malformations (due to environmental or hereditary etiologies), fetal growth retardation and prematurity [16,17,21,22].

Reproductive problems alarm the public, the press, and some scientists to a greater extent than most other diseases. In fact, severely malformed children are disquieting to health care providers, especially if they are not experienced in dealing with these problems. No physician will be comfortable informing a family that their child was born without arms and legs. The objective evaluation of environmental causes of reproductive diseases is clouded by the emotional climate that surrounds these diseases, resulting in the expres-

Table 1  
 Etiology of human congenital malformations observed during the first year of life<sup>a</sup>

| Suspected cause                                                                                                                                        | Percent of total |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| <i>Unknown</i>                                                                                                                                         | 65–75            |
| Polygenic                                                                                                                                              |                  |
| Multifactorial (gene–environment interactions)                                                                                                         |                  |
| Spontaneous errors of development                                                                                                                      |                  |
| Synergistic interactions of teratogens                                                                                                                 |                  |
| <i>Genetic</i>                                                                                                                                         | 15–25            |
| Autosomal and sex-linked inherited genetic disease                                                                                                     |                  |
| Cytogenetic (chromosomal abnormalities)                                                                                                                |                  |
| New mutations                                                                                                                                          |                  |
| <i>Environmental</i>                                                                                                                                   | 10               |
| Maternal conditions: alcoholism; diabetes; endocrinopathies; phenylketonuria; smoking and nicotine; starvation; nutritional deficits                   | 4                |
| Infectious agents: rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella-zoster, Venezuelan equine encephalitis, parvovirus B19 | 3                |
| Mechanical problems (deformations): amniotic band contractions; umbilical cord constraint; disparity in uterine size and uterine contents              | 1–2              |
| Chemicals, prescription drugs, high dose ionizing radiation, hyperthermia                                                                              | <1               |

<sup>a</sup> Modified from [19].

sion of partisan positions that either diminish or magnify the environmental risks. These, non-objective opinions, can be expressed by scientists, the laity or the press. It is the responsibility of every physician to be aware of the emotionally charged situation when a family has a child with a birth defect. The inadvertent comment by the physician, nurse, resident or student in attendance at the time of the child's delivery can have grave consequences for the physician and the family. Comments such as, "Oh, you had an X-ray during your pregnancy", or "You did not tell me that you received an immunization while you were pregnant!" can direct the patient's family to an attorney rather than a teratology or genetic counselor.

**Problem #2.** The second major problem is the inability to arrive at a definitive etiology for reproductive effects such as congenital malformations and spontaneous abortions.

This situation exists because, unfortunately, we do not know with certainty, the causes of congenital malformations and other reproductive effects in all the newborns and children for whom we care. Only a third of the malformed children can be provided a definitive diagnosis and etiology (Table 1).

Lay individuals are unaware of the frequency of reproductive problems. Most pregnant women and some physicians, scientists and even scientific writers are not aware that 15% of known pregnancies result in spontaneous abortion (miscarriage) [23]. These clinical problems occur commonly in the general population and therefore environmental causes are not always easy to corroborate or refute (Table 2). Severe congenital malformations occur in 3% of births. That means that each year in the USA, 120,000 newborns are born with severe birth defects. Genetic diseases contribute wholly or in part to approximately 11% of births. Sponta-

neous mutations account for less than 2–3% of genetic disease. Therefore, mutations induced from preconception exposures of environmental mutagens are difficult endpoints to document [24].

Table 2 lists the frequency of reproductive problems. It is easy to see how unsophisticated lay individuals or even physicians could conclude that a common exposure, such as vaccination, could be responsible for common reproductive problems, if the exposure occurred during pregnancy.

**Problem #3.** Some of the principles of teratology are not applicable to vaccine administration.

It will be apparent that many of the basic principles of teratology are not useful in analyzing the reproductive risks of the most important constituents in live vaccines, i.e. the attenuated viruses. These principles may apply to the other constituents, such as the preservatives, proteins, and polysaccharide antigens. Labeling an agent as teratogenic only indicates that it may have the potential for producing congenital malformations. A 50 mg dose of thalidomide administered on the 26th day postconception has a significant risk of malforming the embryo (Table 3). That same dose taken in the 10th week of gestation will not result in an increased incidence of congenital malformations. One milligram of thalidomide taken at any time during pregnancy will not have a teratogenic effect. We know that X-irradiation can be teratogenic. But if the dose is too low or the embryo is not exposed, there is no increase in teratogenesis [15–17]. The difficulty that occurs when administering attenuated or otherwise modified live vaccines, is that dose may be irrelevant because the antigen can replicate.

When evaluating studies dealing with the reproductive effects of any environmental agent, important principles should guide the analysis of reproductive human and animal

Table 2  
Background reproductive risks

| Reproductive risk                                                                                                                            | Frequency     |
|----------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Immunologically and clinically diagnosed spontaneous abortions per million conceptions                                                       | 350000        |
| Clinically recognized spontaneous abortions per million clinically recognized pregnancies                                                    | 150000        |
| Genetic diseases per million births                                                                                                          | 110000        |
| Multifactorial or polygenic genetic environmental interactions) (i.e. neural tube defects, cleft lip, hypospadias, hyperlipidemia, diabetes) | 90000         |
| Dominantly inherited disease (i.e. achondroplasia, Huntigtons chorea, neurofibromatosis)                                                     | 10000         |
| Autosomal and sex-linked genetic disease (i.e. cystic fibrosis, hemophilia, sickle-cell disease, thalassemia)                                | 1200          |
| Cytogenetic (chromosomal abnormalities) (i.e. Downs syndrome (trisomy 21), trisomy 13, 18, Turners syndrome)                                 | 5000          |
| New mutations <sup>a</sup>                                                                                                                   | 3000          |
| Severe congenital malformations <sup>b</sup> (due to all causes of birth defects: genetic, unknown, environmental per million births)        | 30000         |
| Prematurity/million births                                                                                                                   | 40000         |
| Fetal growth retardation per million births                                                                                                  | 30000         |
| Stillbirths (>20 weeks) per million births                                                                                                   | 2000–20900    |
| Infertility                                                                                                                                  | 7% of couples |

<sup>a</sup> The mutation rate for many genetic diseases can be calculated. This can be readily performed with dominantly inherited diseases when offspring are born with a dominant genetic disease and neither parent has the disease.

<sup>b</sup> Congenital malformations have multiple etiologies including a significant proportion that are genetic.

studies. Paramount to this evaluation is the application of the basic science principles of teratology and developmental biology. These principles are as follows [15–17].

- (1) Exposure to teratogens follows a toxicological dose–response curve. There is a threshold below which no effect will be observed and as the dose of the teratogen is increased both the severity and frequency of reproductive effects will increase.

Live viruses or bacteria do not necessarily follow a toxicological dose–response curve because they may replicate, cross the placenta and replicate in the embryo or fetus (herpes simplex, varicella, VEE, CMV, toxoplasmosis, rubella, syphilis, HIV). Most lived attenuated virus vaccines do not infect the placenta and fetus, but this has to be determined for each new attenuated vaccine. The concept of a no-effect dose would not apply to a teratogenic live virus vaccine, but it would apply to proteins, polysaccharides and

other non-replicating constituents that may be present in vaccines.

- (2) The period of exposure is critical in determining what effects will be produced and whether any effects can be produced by a known teratogen. Some teratogenic effects have a broad, and others a very narrow, period of sensitivity.

The period of sensitivity for replicating infectious agents may not be predictable in some instances. If vaccines with non-replicating antigens produce reproductive effects experimentally, then the sensitive period would have to be determined, in the same manner that the sensitive period is determined for the reproductive effects of drugs and chemicals.

- (3) Even the most potent teratogenic agent cannot produce every malformation.
- (4) Most teratogens have a confined group of congenital malformations that result after exposure during a critical period of embryonic development. This confined group of malformations is referred to as the syndrome that describes the agent's teratogenic effect.
- (5) While a group of malformations may suggest the possibility of certain teratogens, they cannot definitively confirm the causal agent. On the other hand the presence of certain malformations can eliminate the possibility that a particular teratogenic agent was responsible.

These principles are frequently helpful in analyzing individual patient's malformations or epidemiological studies. Examples where clinical evaluations would be helpful are:

- (1) an exposure to a vaccine occurred too late in development to be responsible for a particular malformation;

Table 3  
Developmental stage sensitivity to thalidomide-induced limb reduction defects in the human<sup>a</sup>

| Days from conception for induction of defects | Limb reduction defects                                                                        |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------|
| 21–26 days                                    | Thumb aplasia                                                                                 |
| 22–23 days                                    | Microtia                                                                                      |
| 23–34 days                                    | Hip dislocation                                                                               |
| 24–29 days                                    | Amelia, upper limbs                                                                           |
| 24–33 days                                    | Phocomelia, upper limbs                                                                       |
| 25–31 days                                    | Preaxial aplasia, upper limbs                                                                 |
| 27–31 days                                    | Amelia, lower limbs                                                                           |
| 28–33 days                                    | Preaxial aplasia, lower limbs; phocomelia, lower limbs; femoral hypoplasia; girdle hypoplasia |

<sup>a</sup> Modified from Brent and Holmes, 1983.

- (2) an exposure occurred during pregnancy, but a child is born with a corroborated genetic disease.

### 5. Factors that affect the susceptibility of developmental toxicants

There are a variety of mechanisms by which environmental agents can result in reproductive pathology, which include infertility, congenital malformations, fetal growth retardation, spontaneous abortions, stillbirth and prematurity (Table 4). Very few of these mechanisms could be involved in the potential reproductive effects from immunizing pregnant women.

It would be best if the attenuated virus used in a vaccine never reached the placenta or embryo. Since the main purpose of immunizing the mother is to have her transmit the antibodies to the fetus, it would be best if the antigens used for immunization did not reach the embryo. These theoretical risks appear to be very unlikely, although they will have to be considered and evaluated. It is possible that live virus vaccines could infect the placenta or fetus. Based on the history of modified teratogenic viral vaccines, the risks appear to be very small, although each vaccine would have to be evaluated on an individual basis. The most likely (but remote) mechanisms that might affect the developing embryo and fetus are infection or interference with placental transport. Cytotoxicity and receptor-mediated toxicity (Table 3) are the main mechanisms of most teratogens and these would appear to be very unlikely occurrences following immunization with viral, parasitic or bacterial antigens, unless infection occurred.

One uncertainty is that the “new” protective immunoglobulins resulting from immunization might not be able to be transmitted in significant amounts until the last trimester. In other words, we need studies to clarify the dynamics of immunoglobulin transport to the fetus at various stages of pregnancy.

Another hypothetical risk is the possibility that antibodies produced against foreign proteins and polysaccharides might deleteriously affect the placenta or embryo [25–35]. There is evidence that rarely, autoimmune antibodies may affect the fetus. The complications of lupus erythematosus in pregnant women leading to midgestational pregnancy loss and heart block in the newborn are some examples. Experimentally, investigators have been able to prepare an-

tiserum, which results in serious developmental problems. The teratogenic antiserum produced by Brent [28], Brent and coworkers [29] produced its effect by interfering with the ability of the yolk sac to transmit the necessary amount of amino acids for normal embryonic development [27–35]. The possibility that some infectious agents would produce antibodies that would interfere with embryonic development is remote, but of course possible. Historically, we have the cross specificity of the hemolytic streptococcus antigen and cardiac valve proteins.

### 6. The potential and hypothetical benefits of immunizing women of reproductive age and pregnant women for the purpose of improving their health and reproductive potential, as well as the health of their offspring

- (A) By reducing or eliminating teratogenic and embryopathic congenital infections of the embryo and/or placenta, i.e. herpes simplex, varicella, VEE, CMV, toxoplasmosis, rubella, syphilis, HIV, parovirus B-19, coxsackievirus, hepatitis B, *Borellia* (Lyme disease), malaria.
- (B) By reducing or eliminating neonatal infections acquired during the perinatal or neonatal period for which the neonate has not developed antibodies, i.e. GBS, *H. influenzae* type B, *S. pneumoniae*, *E. coli*, *S. aureus*, etc.
- (C) By reducing intrauterine infections that have been alleged to contribute to premature birth, i.e. *Bacteroides*, *Fusobacterium*, *M. hominis*, *U. urealyticum*, *Campylobacter*, *Clostridium*, *Leptospira*, *T. vaginalis* (bacterial vaginosis).
- (D) By decreasing nursery epidemics from organisms that are considered to be prevalent in environments where antibiotics are used extensively, i.e. *K. pneumoniae*, *F. meningosepticum*, *S. marcescens*, *P. aeruginosa*, *P. mirabilis*, *C. diversus*, *Enterobacter* and *Salmonella* species.

### 7. Lowering the risks of vaccines utilized in pregnant women: studies to be performed

When do you immunize? It will depend on the immunogenicity of the vaccine, the purpose of the vaccine and the

Table 4  
Mechanisms of action of environmental teratogens

|    |                                                                                                                                                        |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | Cell death or mitotic delay beyond the recuperative capacity of the embryo or fetus, (ionizing radiation, chemotherapeutic agents, alcohol)            |
| 2. | Inhibition of cell migration, differentiation and cell communication                                                                                   |
| 3. | Interference with histogenesis by processes such as cell depletion, necrosis, calcification or scarring                                                |
| 4. | Biologic and pharmacological receptor-mediated developmental effects (i.e. etretinate, isotretinoin, retinol, sex steroids, streptomycin, thalidomide) |
| 5. | Metabolic inhibition (i.e. warfarin, anticonvulsants, nutritional deficiencies)                                                                        |
| 5. | Physical constraint, vascular disruption, inflammatory lesions, amniotic band syndrome                                                                 |
| 6. | Interference with nutritional support of the embryo by affecting yolk sac or chorioplacental function or transport                                     |

length of time protective antibodies will persist in the pregnant woman.

Depending on the answers to these questions. Vaccination could be initiated:

1. before pregnancy;
2. first trimester;
3. second trimester;
4. third trimester.

If immunization were to be initiated prior to conception, there might be concern about the impact of the immunization on the developing egg. Sterility, an increase in spontaneous abortion and the induction of genetic disease would be theoretical risks. The genetic effects of preconception exposure to reproductive toxicants (stochastic effects, low risk) would include, dominant mutations, X chromosome-linked mutations, translocations, non-disjunction, deletions and point mutations. The constituents of any vaccine would have to have mutagenic capabilities in order to result in these genetic effects, which would be very unlikely. But allegations of reproductive effects from preconception exposures have been made. Some have scientific merit.

#### 7.1. What do you consider when selecting the appropriate time to immunize pregnant women?

- (1) You would want to select the least vulnerable stage of pregnancy, which will be a difficult task in most vaccination procedures;
- (2) risk to the developing ova and sperm;
- (3) placental transport or transmission of the live attenuated virus or antigen;
- (4) effectiveness of the vaccine: how long will protective levels of antibodies be maintained;
- (5) quantitative determination of the transmission of protective antibodies;
- (6) and frequency of reaction (idiosyncratic or toxic) to the vaccine.

#### 7.2. When should you immunize pregnant women? Appropriate immunization schedules

- (1) Before pregnancy—*Clostridium botulinum* vaccination to prevent infant botulism and vaccination against organisms alleged to be associated with prematurity.
- (2) The first 2 weeks post conception is referred to as the “all-or-none period.” This is the stage before the first missed menstrual period when the embryo is resistant to teratogenic effects but very sensitive to the lethal effects of toxicants. For replicating antigens there is no all or none period.
- (3) Early organogenesis is a stage when the human embryo is undergoing the development of the major organs, from the 16th to 40th post-conception day. Major malformations of the brain, eyes, ears, limbs, lungs, heart, kidney, some craniofacial malformations, etc., can be induced

during this period. Important CNS malformations include neural tube defects (NTD), deafness, eye malformation, autism and an absent corpus callosum can also be induced at this early stage. This is probably the most inappropriate stage for immunization, not because the risk of reproductive failure is increased, but because this is the stage where such an allegation places the vaccinator and the vaccine at greatest risk.

- (4) Late organogenesis, early fetal development, is a stage when cleft palate, genitourinary malformations, microphthalmia, and hydrocephalus can still be induced from the 40th to 60th day, post conception.
- (5) Midgestation, from the 8th to 15th week, is a stage most vulnerable to interference with neuron proliferation, differentiation and migration in the brain, which can result in microcephaly. Abnormal genital organ differentiation and permanent fetal growth retardation is most severe during this stage.
- (6) Late fetal development: occurs during the latter part of the second trimester and third trimester and is susceptible to alterations in CNS maturation and growth, growth retardation of the fetus or specific organs. Hypothetical CNS effects include, cerebral palsy, epilepsy, ADHD, psychiatric disorders, infarcts, congenital strokes, mental retardation, autism and other neurological abnormalities. These problems are not uncommon and represent a significant risk to anyone administering medications or vaccines during this period, even though there is little data to confirm the intrauterine causes of these effects. This is the best stage for immunization if efficient transport of protective antibodies is the vaccinator’s main goal.

#### 7.3. Spontaneous abortion

There is no more treacherous area of epidemiology research than studies, which involve solely the evaluation of abortion risks of environmental agents, without the simultaneous evaluation of other reproductive parameters. Since approximately 15% of documented pregnancies terminate in spontaneous abortion and a much larger number of embryos are lost before the first missed menstrual period [23,36–38] this is a reproductive effect that is very common (Table 2). Allegations that environmental toxicants are responsible for spontaneous abortions are frequently made. It is a very complex subject, which cannot be dealt with adequately in this paper, except to state that it is a difficult allegation to debate and there are numerous genetic, maternal disease states and environmental causes of abortion. Drugs and chemicals contribute minimally to incidence of abortion.

Very few studies dealing with abortion consider the complexity of performing competent epidemiology research. This creates a serious dilemma for health care providers when a therapeutic intervention, i.e. if a particular immunization, was alleged to be responsible for increasing the abortion rate.

## 8. Summary

### 8.1. Attempts to establish successful programs of immunizing pregnant women

Establishing successful vaccine programs for pregnant women would be the quintessence of preventive medicine when you realize their disease preventive potential. The success of this initiative will depend on a number of components and participants:

- (1) The development of vaccines to prevent or reduce reproductive effects using modern molecular biological tools will necessitate extensive research programs that will identify the antigenic components that induce protective antibodies against the various infectious agents or the modification of pathogenic viruses to confer immunogenicity without pathogenicity. The necessary studies will include: (a) the determination of the effectiveness of the vaccines in producing protective antibodies; (b) whether there is transmission of protein and polysaccharide antigens to placental and/or embryonic tissues; (c) the initiation of pre-clinical studies with regard to reproductive effects; (d) the evaluation of the vaccines for idiosyncratic or other pathological effects; and (e) the initiation of clinical trials.
- (2) Before initiating the development of vaccines for the prevention of prematurity, further studies (epidemiological and bacteriological) are necessary to document whether the organisms that have been suggested to cause intrauterine infections result in prematurity.
- (3) It is important that the Governmental agencies that are responsible for approving vaccine licensing should be involved in the development of these new vaccines. Their advice and involvement on legislation and public education should be sought. The press also has to be educated about the purpose and benefits of this group of vaccines and the benefits that could be obtained from the successful introduction of this group of vaccines. The public needs much more input from the scientific community and governmental agencies with regard to the benefits of immunization just before or during pregnancy, as well as the background incidence of the array of reproductive risks.
- (4) Legislation was required in the USA to attempt to rectify the deluge of litigation claiming injury secondary to vaccination in children. The vast majority of these claims for injury were not valid. Even after the legislation creating the Vaccine Compensation Injury Act non-meritorious claims continue to be filed. The litigation costs and insurance costs have escalated, as have the cost of vaccines. These problems were created by the filing of non-meritorious lawsuits by the plaintiff's bar. Therefore a solution to these litigation problems should be sought in advance [39–46].
- (5) There has been minimal *interaction with the legal profession* to address the escalation of vaccine injury litigation and the cost of vaccines. Obviously, in the USA, appealing to the American Trial Lawyer's Association would be futile. But the American Bar Association or the Legislatures may be able to provide remedies that would permit the immunization of pregnant women to succeed, at least on an economic basis. Removing the injury claims from the courts has been an improvement, but the situation is still unacceptable. All you have to do is search the internet and count the number of law firms advertising for vaccine injury litigation cases ([www.vaccine.injury.com](http://www.vaccine.injury.com)) [39,47]. The potential risks to the mother and infant of immunizing pregnant women just before becoming pregnant or during pregnancy are theoretical, but are probably very small. New vaccines for pregnant women will have to be monitored very carefully. The greatest problem will come from attorneys (in the USA) and anti-vaccine constituencies around the world. The potential for vehement animosity and litigation is probably greater with regard to pregnancy than controversies involving vaccinated children and adults.
- (6) One problem that needs to be addressed by the scientific and medical community is the number of *irresponsible expert witnesses* that are willing testify in non-meritorious vaccine injury lawsuits [39–48]. Not only do these individuals contribute to the escalation of litigation and the increased cost of vaccines but they also demean the scientific and medical community. The Public has labeled scientists and physicians as individuals with integrity and high ethical standards. This should be a cherished gift that has been bequeathed to scholars by Society [49]. It is gift that can be withdrawn, because of the activities of scientists who commit fraud or testify irresponsibly. We are not doing enough to monitor and academically chastise this unscrupulous group of “experts” [39–49].

We have a great deal of work in the areas of the development and perfection of vaccines administered before and during pregnancy, but success could result in a tremendous improvement in pregnancy outcome and infant survival and health. We have to be more diligent and forceful in counteracting those special interest groups that persist in miss-educating the public as well as those who pursue a course for their own financial gain against the best interests of the public at large. The regulatory agencies and the vaccine producers will need a great deal of objective scientific advice and support and it is our responsibility to provide that support.

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