PASSIVE IMMUNIZATION FOR IMMUNOCONTRACEPTION: LESSONS LEARNED FROM INFECTIOUS DISEASES

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1. ABSTRACT

Development of vaccine for contraception is an exciting proposition that could provide a valuable alternative to the presently available methods for birth control. Various targets such as gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH), leutinizing hormone (LH), zona pellucida (ZP) antigens, sperm antigens, and human chorionic gonadotropin (hCG) are being explored for immunocontraception. Besides specific concerns associated with each contraceptive vaccine, the progress has been restricted by the variability of the immune response after active immunization, attainment and maintenance of high antibody titers, time lag to achieve reasonably good antibody titers, and uncertainty regarding how long the bioeffective antibodies will remain in circulation. It is envisaged that these concerns may be taken care of by using the preformed antibodies in the passive immunization approach. The antibody therapies have been tried and found to be successful against various infectious diseases both in animals as well as humans. Some have become treatment modalities in the clinics. This manuscript will review the data available for the passive immunization of preformed polyclonal and murine/human monoclonal antibodies, their efficacy, mode of delivery, duration of the effects, and limitations, if any. The overall objective is to examine the feasibility and practicability of the passive immunization approach for immunocontraception.

2. INTRODUCTION

Development of new contraceptive technologies is important considering the worldwide population explosion and abortion rates. The world population has exceeded 6.353 billion and it is taking approximately 12 years to add 1 billion to the population (1). Ninety-five percent of this growth is in underdeveloped countries. Besides population explosion, unintended pregnancies are a major public health issue. It is estimated that each year there are approximately 210 million pregnancies worldwide, of which twenty-two percent, over 46 million, end in abortions. Even in the United States, annually, half of all pregnancies are unintended, resulting in over 1 million elective abortions (2). In over half of these pregnancies, the women were using some type of contraception. Thus, there is an urgent need for better methods of contraception, which is acceptable both in the developing and developed countries.

Contraceptive vaccines (CVs) have been proposed as a valuable alternative. CVs may be more acceptable than the currently available methods due to high specificity, limited or no side effects, low cost, and infrequent administration. Various targets such as gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH), leutinizing hormone (LH), zona pellucida (ZP) antigens, sperm antigens, and human chorionic gonadotropin (hCG) are being explored for immunocontraception (3). The hCG vaccine has undergone phase I and phase II clinical trials in women (4). Besides specific concerns associated with each vaccine, the progress of the development of CVs for each of these targets has been hampered by the following facts. These include: 1) variability of the immune response among the vaccinated individuals, 2) attainment and maintenance of high titers of antibodies for bioefficacy, 3) time lag from the first injection to the time to achieve reasonably good antibody titers, that generally takes 3 months, and 4) uncertainty regarding how long the antibody titer will remain in the circulation to exercise the contraceptive effects. These concerns are associated with the active immunization studies involving these vaccines. It is envisaged that these concerns may be taken care of using the passive immunization approach. The present article will review the data available for the passive immunization of preformed antibodies, their efficacy, mode of delivery,
duration of the effects, and limitations, if any.

3. DISCUSSION

3.1. Historical perspective of passive immunization studies for protection against infectious diseases

Historically, the use of preformed antibodies for protection against specific diseases was demonstrated in the 1890s by the administration of animal sera to infected children for treatment of diphtheria (5). Subsequently, the rabbit and horse immune sera were used for the treatment of pneumonia, meningitis, diphtheria, and other diseases (6). The significant toxicity, as manifested by serum sickness, anaphylaxis, and sensitization to heterologous proteins, limited its widespread use and acceptability. The use of human instead of animal sera containing enough high antibody titer to eliminate these problems was limited by practical and ethical constraints. At the end of the World War II, the human plasma was used for intramuscular (im) injections to prevent the outbreak of red measles and hepatitis infection in US soldiers (7). In 1952, Burton used im injections of human plasma derived IgG to increase the IgG levels in agammaglobulinemic patients (8). Treatment resulted in a reduction in number of serious bacterial infections. Subsequently, human γ-globulin preparations purified from sera were injected im to prevent paralytic disease caused by polio (9). In the 1970s, it was observed that one could achieve 70-100% efficacy in preventing transmission of hepatitis B by administration of immunoglobulins to neonates born to infected mothers (10). The safe im doses were limited to about 100-150 mg/kg body weight (11). These preparations were not completely safe for intravenous infusion and produced severe anaphylactic reactions. To overcome the dosage limitation and make it safe for intravenous delivery, further purification of antibody preparations was required. Soon improvement in antibody purification methods (12), the development of hybridoma technology (13), and molecular engineering strategies to modify murine monoclonal antibodies (Mab) to humanized monoclonal antibodies or creating mouse-human chimeras led to the development of better immunoglobulin preparations for human administration. Polyclonal human immunoglobulins containing 90-100% IgG class are active in neutralizing several bacterial, viral, mycoplasmic and fungal antigens (Table 1). Hepatitis B immunoglobulin (human) is approved in the United States for prevention of hepatitis (BayHepB™ and Nabi-HB™). Similarly, several more “human” immunoglobulin (Ig) molecules are now approved in the United States for treatment against hepatitis A (BayGam™), cytomegalovirus (CytoGam™), rabies (BayRah™ and IMOGAM™), tetanus (BayTet™) and several other diseases.

3.2. Bioefficacy of various classes of immunoglobulins for passive immunization

Depending on the application, any class of immunoglobulin (IgG, IgA, IgM, IgD or IgE) could be used for passive immunization (9). The first consideration is the intravascular half-lives (TI/2) of these molecules. These have been investigated in several species using radiolabeled immunoglobulins (14). The catabolic rate varies inversely with the size and metabolic rate of the host. Generally a two-phase serum disappearance is seen with initial rapid clearance followed by a slower intravascular decay representing actual catabolism. Human IgG has the longest TI/2 (21 days) followed by IgA (6 days), IgM (5 days), IgD (2.8 days) and IgE (2.7 days). Within a class, the subclasses can have different TI/2 values. For example, in the IgG class, IgG3 has the shortest TI/2 of 7.1 days, while all subclasses of IgA have similar TI/2. These TI/2 values have also been validated by using biosynthetically labeled 35S immunoglobulins. In contrast to the intact immunoglobulin molecule, the clearance of free Fab fragments from circulation is very rapid, filtering out into the urine. TI/2 values of different murine antibody classes/fragments, when injected into humans, vary from 1 - 18 hr. F(ab')2 also tends to be cleared rapidly (24 - 31 hr), but to a lesser degree than the Fab. The equine Fab against rabies virus has a TI/2 of 50 - 70 hr after intramuscular injection (15).

Other considerations in selection depend upon the specific application of that particular class of immunoglobulin. IgG with a serum half life of about 21 days is suited for prolonged activity in systemic applications. The transplacental transport of the IgG class can be useful for imparting immunity to newborns. For mucosal applications, polymeric IgA is the suitable choice since it is the predominant antibody class in most mucus secretions. IgM could be the class of choice if complement-mediated action is required. Antibody engineering techniques could be used to produce a class switch for a passive immunization strategy that is best suited for a particular application.

3.3. Efficacy of various routes of antibody administration

The effectiveness of the antibodies is contingent upon their stability in the environment in which they are administered and have to function. The advantage of passive immunization regarding directly delivering antibodies to the site of action would be negated if they were not stable at that particular site. In general, the immunoglobulins are stable proteins capable of functioning in various parts of the human body. They are active in the sweat, mucosal secretions, and in the protease-rich environment of the stomach (pH 2.0) as well as in semen, tears, and gastrointestinal fluids (pH 8.0). The antibodies are capable of binding antigens in wide pH range (pH 4.0-9.0) (16). Different workers have tested oral, nasal and vaginal routes for efficacy of passively administered antibodies.

Passive immunotherapy against enteric pathogens requires oral administration for best results. The oral delivery of bovine immunoglobulins in humans results in survival of ~50% of total immunoglobulins after passage through the stomach and the small intestine (17). This study was conducted on six volunteers undergoing ileostomy, who were fed bovine immunoglobulin concentrate (BIC- Clostridium difficile), having high titters of neutralizing IgG antibodies, prepared from the colostrum of cows. C. difficile is a pathogen whose exotoxin produces diarrhea and colitis. The volunteers were fed ~2.1 g of bovine IgG and ~1.03 g were recovered in the ileal fluid. The IgG recovery was not increased after using antacid or
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omeprazole. The toxin neutralizing activity correlated well with the IgG levels. Earlier studies had shown detectable levels of bovine IgG as well as C. difficile toxin neutralizing activity in the stools after oral BIC-C. difficile administration (18). In these studies, the fecal bovine IgG levels were found to increase when oral BIC-C. difficile was administered in enteric-coated capsules. Prolonged gastrointestinal transit time was shown to reduce bovine IgG recovery from 76% to 31% when the transit time increased over two hours. Similar results have been obtained for the prevention of gastro-intestinal infections by using milk immunoglobulin concentrates with high antibody titers against enterotoxic Escherichia coli (19) and Shigella flexneri (20), and for rotavirus infection using bovine antibodies (21) and human immunoglobulins (22).

One of the most successful examples of prophylactic and therapeutic intervention has been antibody delivery to the respiratory mucosal surfaces (nasal drops/ aerosol/ nasal spray) for common viral infections such as coxsackie, influenza, rhinovirus and RSV (23) (Table 1). In nasal drop treatment, seronegative individuals were administered with six daily doses of gammaglobulin from one day before virus challenge to four days after challenge. It significantly reduced the upper respiratory infection on challenge with coxsackie virus (24). Similar gammaglobulin treatment, via nasal and oral routes, showed lower infection with seroconversion rate compared to control human (25). Nasal sprays of human IgA (IgAbulin), administered twice daily for 17 days, decreased upper respiratory illness in cross-country ski-team athletes (26). Similarly, children treated with nose drops of IgA had reduced upper respiratory tract infection and rhinitis while on treatment (27, 28). An anti-RSV human antibody (RespiGam™) is commercially available for intravenous injection. The study of the protective effect of intranasal RespiGam™ treatment on cotton rats showed the effect to be similar to that of parental treatment, but required a much lower dose (29). Medi-493 (Palivizumab™) is another humanized monoclonal antibody developed for parenteral immunization that could also be delivered intranasally (23). A small-scale human study showed that a monthly dose of 10-15 mg/kg is sufficient to maintain the target level of neutralizing antibody (30). HNK 20 is a mouse monoclonal IgA antibody against the RSV-F glycoprotein developed specifically for intranasal passive immunization. Intranasal administration of adults, healthy infants and high-risk infants, followed by intranasal challenge with wild type RSV group virus, showed a lower mean daily virus shedding than the non-immunized controls, during acute virus infection (23). The Fabs were as effective as the intact antibodies for therapeutic efficacy (31).

The mucosae of female and male genital tracts are important entry ports for sexually transmitted diseases (STDs). The secretions of female and male genital tracts differ from other external secretions for immunoglobulin classes, isotype specificities and concentrations. The predominant immunoglobulin (Ig) in genital tract secretions is secretory-IgA (S-IgA) followed by IgA, IgG and IgM. The various classes of immunoglobulins are stable in secretions of male and female reproductive tracts (32). The purified immunoglobulins (S-IgA, IgA, IgG and IgM) were incubated in a pool of fresh seminal plasma (SMP) and cervical fluid at 37°C for up to 48 h and analyzed for stability and integrity by the immunodiffusion, immunoelectrophoresis and radial immunodiffusion. Radiolabeled 125I-Ig preparations were incubated similarly and samples were chromatographed on Sephadex G-150 column. The elution patterns of each Ig and their functional activity were analyzed for anti-toxic activity against tetanus toxoid (32). All these antibody classes including S-IgA, IgA and IgG were immunologically and functionally stable in the presence of SMP and cervical fluid. The proteolytic activities of these genital tract secretions did not degrade the immunoglobulins. Appearance of IgG antibody in the reproductive fluids following parenteral immunization and its stability in the genital tract secretions suggests its use as a suitable therapeutic agent for protection against local infection and immunocontraception. Antibodies delivered to the vaginal mucosa have been reported to protect mice against genital herpes infection (33). The vaginal delivery of a cocktail of monoclonal antibodies against sexually transmitted disease (STD) pathogens might be a quite effective method against STDs (34).

3.4. Are there any immunopathological consequences of passive immunization therapy?

Homologous antibody preparations are preferable to heterologous preparations because they lack hypersensitivity reaction and serum sickness. However, they are more expensive. Heterologous antibody preparations are still used for certain conditions such as anti-venom therapy because of the practical reasons of non-availability of the human antibodies. In contrast to intact immunoglobulins, antibody fragments such as Fab are better choices for several purposes such as toxin neutralization, receptor blocking and drug chelation, as well as non-immunogenicity. On administration of whole murine Mab, F(ab)’, and Fab in humans, the anti-mouse antibody development was 53%, 83% and 2% respectively (35).

One of the major limitations of passive immunization is the determination of dosage for the efficacy of the therapeutic sera in humans. The mouse model can only provide a rough estimate for efficacy in humans. Toxicity such as allergic reaction and serum sickness associated with antibody therapy is due to the use of polyclonal heterologous preparations. Administration of murine antibodies in patients with human anti-mouse antibodies result in immune complex formation causing serum sickness or renal toxicity (36). Mouse-human chimeric antibodies are less immunogenic than murine antibodies but still elicit significant human anti-chimeric antibodies. After administration of chimeric antibody to TNF-α, (Infliximab™) for treatment of rheumatoid arthritis, the percentage of patients that developed serum antibodies was 53%, 21% and 7% when 1 mg, 3 mg and 10 mg antibody/kg body weight was administered respectively (37). Humanized or CDR-grafted antibodies are less
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Table 1. Successful antibody therapies in humans against infectious diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine (TM)</th>
<th>Administration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Human purified Immunoglobulin/serum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>Tetanus Immunoglobulin (TIG) (BayTet™)</td>
<td>Intramuscular (IM)</td>
<td>250 neutralizing units/kg body weight</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B (HBIG) (BayHep B™)</td>
<td>IM</td>
<td>0.06 ml/kg body weight (Booster after 3 months)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B (HBIG) (Nabi-HB™)</td>
<td>IM</td>
<td>Dosage as BayHep B™</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Hepatitis A IG (BayGam™)</td>
<td>IM</td>
<td>0.02 ml-0.25 ml/kg</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Hepatitis C Immunoglobulin</td>
<td>IM immunization clinical trials</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>HIV</td>
<td>HIV Immunoglobulin</td>
<td>IM immunization clinical trials</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immunoglobulin (RIG) (Imogam Rabies-HT™)</td>
<td>IM</td>
<td>20 International units/kg body weight</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies (RIG) (BayRab™)</td>
<td>IM</td>
<td>20 IU/kg</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>Varicella-zoster IG</td>
<td>IM</td>
<td>125 U/10 kg (Max. 625 units)</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td>Respiratory Syncytial Virus (RSV-IGIV) (RespiGam™)</td>
<td>Intra venous (IV)</td>
<td>750 mg/kg body weight</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus (RSV-IGIV) (RespiGam™)</td>
<td>Nasal spray</td>
<td>Clinical trials (3 ml of 1:20 inhibition titer)</td>
</tr>
<tr>
<td>Common cold</td>
<td>Influenza virus Ig</td>
<td>Nasal aerosol</td>
<td>Preliminary Trials (50 mg/kg)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Cytomegalovirus Immunoglobulin (CMY-IGIV) (CytoGam™)</td>
<td>IV</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>Antibody deficiency</td>
<td>IVIG</td>
<td>IV</td>
<td>160 mg-640 mg/kg body weight</td>
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<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>IVIG</td>
<td>IV</td>
<td>1280 mg/kg body weight</td>
</tr>
<tr>
<td>Premature newborns</td>
<td>IVIG</td>
<td>IV</td>
<td>400 mg/kg at weekly or biweekly intervals</td>
</tr>
<tr>
<td>Post surgical prophylaxis</td>
<td>IVIG</td>
<td>IV</td>
<td>400 mg/kg/week</td>
</tr>
<tr>
<td>Haemophilus influenza (Type B)</td>
<td>Immunoglobulin</td>
<td>Preliminary Clinical trials (Dosage and route not described)</td>
<td>Not described</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Immunoglobulin</td>
<td>IV</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>Streptococcus (Gmp B)</td>
<td>Streptococcus Ig</td>
<td>IV</td>
<td>1-2 mg/kg</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>Vaccinia immunoglobulin (VIG)</td>
<td>IV</td>
<td>Not described</td>
</tr>
<tr>
<td><strong>B) Human/Humanized monoclonal antibody (Mab)</strong></td>
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<tr>
<td>RSV</td>
<td>RSV-IGIM (Palivizumab™)</td>
<td>IV</td>
<td>10-15 mg/kg body weight</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>Rhinovirus Mab</td>
<td>Nasal drops</td>
<td>Preliminary Trials (Dosage varies)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Human monoclonal antibody</td>
<td>IM immunization clinical trials</td>
<td>Dosage not described</td>
</tr>
<tr>
<td><strong>C) Human purified IgA</strong></td>
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</tr>
<tr>
<td>RSV</td>
<td>RSV IgA</td>
<td>Nasal drops</td>
<td>Preliminary trials (varying dosage)</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>IgAbulin</td>
<td>Nasal spray</td>
<td>Preliminary trials (Dosage varies)</td>
</tr>
<tr>
<td><strong>D) Porcine Immunoglobulin</strong></td>
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<tr>
<td>HIV</td>
<td>HIV Immunoglobulin</td>
<td>IM Preliminary trials</td>
<td>Not described</td>
</tr>
<tr>
<td><strong>E) Equine purified immunoglobulin</strong></td>
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<tr>
<td>Immunosuppressive therapy</td>
<td>Lymphocyte immunoglobulin (argin™)</td>
<td>IV</td>
<td>Dosage not described</td>
</tr>
<tr>
<td><strong>F) Recombinant antibody Fab fragment</strong></td>
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<td></td>
</tr>
<tr>
<td>Snake bite</td>
<td>Crotalus snake venom Ovine Fab (CroFab™)</td>
<td>IV</td>
<td>Three doses of 6 hours interval based on neutralizing potential</td>
</tr>
<tr>
<td><strong>G) Bovine milk concentrate hyperimmunoglobulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Hyper immunoglobulin</td>
<td>Oral immunization trials</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>Crypctobacterium</td>
<td>Hyper immunoglobulin</td>
<td>Oral immunization trials</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Hyper immunoglobulin</td>
<td>Oral immunization trials</td>
<td>Dosage not described</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>Hyper immunoglobulin</td>
<td>Oral immunization trials</td>
<td>Dosage not described</td>
</tr>
</tbody>
</table>

1 Data compiled from Communicable disease control immunization program report and references 11, 23, 76

immunogenic than mouse-human chimeric antibodies (38). Human monoclonal antibodies can also elicit antibody response. Infusion reactions are common adverse effects after human Mab administration, and severe infusion reactions can occur after administration of several antibodies due to release of several cytokines (39). Anti-TNF-α therapy with Infliximab™ can result in the appearance of serum antibodies to double stranded DNA (37). It can therefore be concluded that the toxicity of antibody preparation depends on the class, subclass, valency, kinetics, and the antigen and species specificities of antibody preparations. There is no report in literature on the development of anti-idiotypic antibodies even after repeated injections of homologous antibodies (intact or (Fab′)2 or Fab) even after a prolonged period of injection, without using any adjuvant.

3.5. Clinical applications of passive immunization in infectious diseases

Passive antibody therapies can have a wide range of applications in either enhancing or suppressing the immune function, which cannot be achieved by any other
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drug. It can have tremendous clinical applications both in enhancing the immune function to help increase the host defense against infectious agents, and in suppressing the immune function required for certain clinical situations such as autoimmune diseases, antisperm antibody-mediated infertility and organ transplantation technology. The passive antibody therapy can also be used for toxin neutralization such as treatment of diphtheria toxins, tetanus, botulism and snake venoms. Antibody preparations are in use for viral neutralization in hepatitis B, varicella-zoster, cytomegalovirus, rubies and respiratory syncytial virus (RSV) infections (Table 1). Autoimmune clinical symptoms can be suppressed by antibody administration specific to various immune components. Infliximab<sup>TM</sup>, a chimeric IgG1 Mab to TNF-α, neutralizes TNF-α activity resulting in significant reduction in the gastrointestinal inflammation in Crohn’s disease (40) and joint inflammation in rheumatoid arthritis (37). Another mouse-human chimeric antibody, designated as c7E3, against human platelet glycoprotein IIb/ IIIa is used during angioplasty for arterial closure prevention (41). Muromonab CD3<sup>TM</sup> and Daclizumab<sup>TM</sup>, that targets human CD3 antigen in the T cells (39) and high affinity IL-2 receptor (42) respectively, are used in the prevention of organ rejection after transplantation. The antibodies that are specific to developmental antigens on neoplastic cells are useful in cancer therapy (43).

The intravenous immunoglobulins (IVIG) treatment, containing IgG, is recommended for infants whose mothers have hepatitis A, measles or poliomyelitis infection at or near time of parturition (44), though its effect on prophylactic effect is debatable. Studies in cotton rats in the 80s demonstrated a significant reduction after IVIG treatment in the in vivo RSV replication in the nasal mucosa and lungs (45). Based on the animal data and human studies, the human polyclonal RSV IVIG (RespiGam<sup>TM</sup>) and humanized mouse Mab (Polyvizumab<sup>TM</sup>) have been approved as prophylactic treatment for infants and children having lung disease, given within six months before the RSV season begins. Studies also demonstrate that IVIG infusion reduces serious CMV infection in liver and kidney transplants (46). Studies on macaques (47) demonstrate that high titers of neutralizing antibodies, administered intravenously, protect mucosal surfaces against challenges with high doses of human immunodeficiency virus (HIV). IVIG therapy with anti-viral therapy is beneficial in infants and children with acquired immunodeficiency syndrome (AIDS) who have IgG levels lower than 250 ng/dl to prevent serious bacterial infection (48). Antibodies can be administered systemically for protection up to a few months. If the antibodies are released slowly over a longer period of time using the polymer technology, a long-term protection can be provided (49).

The expense and high specificity of the antibody therapy limits its application to conditions where no drug exists or where the conventional drug therapy is not effective. The hybridoma technology and antibody engineering strategies have provided specific humanized monoclonal antibodies that can be used instead of polyclonal sera (50). This overcomes the shortcomings of IVIG preparations because it will decrease the amount of antibodies to be administered and at the same time increase the target specificity. Also, the risks involved due to blood borne contaminations are eliminated. A humanized IgG, Synagis<sup>TM</sup>, the first monoclonal antibody available for the prevention of RSV infection, is reported to be 50 times more potent than the polyclonal preparation of RespiGam<sup>TM</sup> (51). Topical applications of monoclonal antibodies and recombinant IgA have been used to prevent bacterial colonization of the oral cavity (52). The synthesis of monoclonal antibodies in plants, the plantibodies, is very exciting and assures cost-effectiveness for production of large quantities (53).

3.6. Clinical applications of passive immunization in immunocontraception

As discussed above, besides specific concerns associated with each contraceptive vaccine, the progress of the development of CVs for several targets in the active immunization approach has been restricted by the variability of the immune response, attain and maintain high antibody titers, time lag to achieve reasonably good antibody titers, and uncertainty regarding how long the antibodies will remain in the circulation. It is envisaged that these concerns may be taken care of using the passive immunization approach. The data discussed above for the passive immunization, that has been quite successful for various infectious diseases, indicate that such an approach might also be a feasible and viable proposition for immunocontraception.

Vaccines for contraception target a molecule, which has an important but specific role in reproduction. The target antigens must be accessible on the cell surface (sperm or oocyte proteins) and can be secretory molecules (hormones). These antibodies either neutralize the secretory molecules, blocking the receptor-ligand interactions as in hormones, or inhibit the gametes function and/or the binding of sperm-egg binding, blocking the fertilization process. For blocking sperm-egg interaction, the neutralizing antibodies must be present in the reproductive tract, probably also in the circulation. The data from various laboratories indicate that to have a contraceptive effect, both the circulating as well as local antibodies are important (54). The cervical mucus has IgG and a lower concentration of IgA antibody (55) and complement components (56). The oviductal fluid also has IgA and IgG, probably from transudation of antibody from serum (57). Immunohistochemical analysis indicates high concentrations of immunoglobulin-secreting cells in uterine endocervix than any other region of the reproductive tract (58). Information is available on the levels of immunoglobulins during menstrual cycle, their isotype distribution, and their physiochemical properties. The distribution of the antigen presenting cells in the fallopian tubes, uterus and vagina has also been investigated (54, 58, 59).

The male genital tract secretions also have IgG, IgA and IgM classes of immunoglobulins, with higher levels of IgG and IgA in the ejaculates (60, 61). In the
The antibodies against the target antigens should be present in the vagina to provide significant immunoprotection from pregnancy as well as STDs. As discussed above, the antibodies are stable in seminal fluid and in cervical mucus at 37°C for at least two days (32). These mucosal antibodies could provide protection for one day to several days since the effective half-life of the antibody is dependent on the turnover time of mucus (71). This guarantees the reversibility of contraceptive effect, but for continued protection the antibodies need to be replenished at constant intervals, if required. The recombinant DNA and antibody engineering technologies can help to produce human/humanized intact immunoglobulins or various functional fragments, such as Fab or scFv in large amounts in vitro that could make its repetitive use feasible without serious side effects. The antibodies can be delivered in gels and sustained release devices for continued protection (72). In this study, an intra-vaginal device composed of polyethylene-co-vinyl acetate was tested in vagina of mice. It resulted in continuous release of functionally intact IgG for over 30 days. The immunoglobulins were released through a water filled pore network by diffusion at a release rate of ~0.1-1.0 mg total protein per day, providing nearly constant mucus levels of protective antibody (72).

The use of antibody therapy should not raise any autoimmune or an anti-idiotypic immune response. The immunoglobulins causing a contraceptive effect could be combined with antibodies against STDs to have a dual protective effect. Also, immunoglobulins against various contraceptive target epitopes could be combined in a single formulation to have a strong and sure shot protection against pregnancy. Although much work has been done regarding the clinical efficacy of the antibody therapy in the infectious diseases, nothing much has been investigated in the field of immunocontraception. There is only some sparsely available data, discussed above, in some animal models regarding the contraceptive efficacy of some mouse monoclonal antibodies or polyclonal antibodies, administered passively via intraperitoneal, intramuscular, intravaginal, or intravenous routes. Recently, there has been some interest to humanize the murine monoclonal antibodies or to raise human monoclonal antibodies against various contraceptive epitopes (73-75). These antibodies and additional antibodies that are being engineered await trials in animal models and in humans for demonstration of efficacy, duration, and reversibility of the antifertility effects. The data from antibody therapies including clinical trials in infectious diseases indicate that it is an exciting, practical, viable and durable proposition ready for experimentation.

4. ACKNOWLEDGEMENT

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5. REFERENCES


Passive immunization for immunocontraception

**Microbes Infect** 2, 701-708 (2000)


33. Whaley, K.J, L. Zeitlin, R. A. Barratt, T. E. Hoen and
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