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Pregnancy and immunity

Changes occur, but pregnancy does not result in immunodeficiency

For mammalian pregnancy to succeed, large physiological adjustments are required in the mother: these changes result from signals passing between the conceptus (especially the trophoblast) and the mother throughout pregnancy. Every system in the body is affected, including the immune system, which is part of a complex signalling system between cells that has developed the ability to recognise self and non-self.

Immune adaptation is not required for the mother to cope with the fetus as an allograft. The lack of HLA antigens on the syncytiotrophoblast and the presence of only the non-classic HLA G antigen on the cytotrophoblast cells precludes the fetal trophoblast from playing any part in currently recognised types of allogeneic immune reactions.¹ All these reactions depend on the cellular recognition processes associated with the major histocompatibility complex classes I and II. Not only, therefore, will the maternal immune system fail to be stimulated by allogeneic trophoblast, but allogeneic trophoblast cannot be the target for otherwise armed maternal cytotoxic T cells. Furthermore, according to current understanding of the phenomenon of "major histocompatibility complex restriction," the absence of classic major histocompatibility complex antigens on the trophoblast will prevent the corecognition of any other form of cell surface antigens that it might express. The mother is not "immunodeficient": in terms of classic mechanisms dependent on T cells she remains immunocompetent throughout pregnancy.²

The maternal immune response does, however, undergo some changes. Data from inbred mice and less good evidence from human pregnancy (reviewed by Wegmann *et al*)³ suggest that the maternal immune response may be modulated away from cellular responses towards humoral immunity, not all of which depends on recognition of major histocompatibility complex antigens. For example, antibody production during pregnancy tends towards the IgG 1 isotype and away from the complement fixing IgG 2a isotype, particularly for antibodies against fetal alloantigens. In addition, cytotoxicity mediated by non-specific natural killer cells, seems to be dampened by inhibition by the TH1 helper cells, which produce cytokines such as interleukin-2 and interferon gamma. Activation of natural killer cells in pregnant mice is known to result in fetal resorption. This suggests that the bias towards the production of helper cells in pregnancy may be a protective mechanism tending to promote fetal survival. Dudley *et al* have observed that the cytokines produced by activated lymphocytes during murine pregnancy tend to favour antibody production over cytotoxic responses.⁴ This effect is most prominent within the uterine decidua, but it also has systemic effects. Dudley *et al* also contend that the regulation of cytokine production during normal pregnancy changes as a result of the pregnancy itself and not in response to specific fetopaternal antigens.

Another possible immune modification might be some adaptation to inhibit non-specific complement mediated damage to trophoblast. Holmes and Simpson have shown that

this is achieved at the level of the trophoblast itself without requiring any systemic dampening of the complement cascade, which presumably needs to remain intact if the mother is to combat infections adequately.⁵ The human trophoblast expresses three membrane bound complement regulatory proteins, which protect it from maternal complement mediated damage arising not only from activation of the classic or alternate pathways but also after systemic complement activation in response to microbial infection.

Do the changes in the immune system during pregnancy have any untoward clinical effects? There is little firm scientific evidence that pregnant women are more susceptible to infectious diseases.⁶ In general, neither viral nor other infections (such as tuberculosis) seem to occur more commonly in pregnancy, nor are localised infections more likely to become generalised, as occurs in immunosuppressed patients. Clinical experience suggests that varicella infections tend to be more severe during pregnancy—in particular, varicella pneumonia seems more common in pregnant women, but this might be related to the mechanical effects on the diaphragm of the enlarged uterus.⁷ Falciparum malaria may be more common and severe during pregnancy, particularly during a first rather than subsequent pregnancies.^{8,9}

The potential effects of pregnancy on HIV infection and AIDS are of growing concern. Current evidence does not suggest that pregnancy makes any difference to the natural course of HIV infection in women.¹⁰ Access to medical care, particularly for drug using women, seems to be a more important determinant of outcome than pregnancy. This is, however, only an interim judgment.

The misconception that pregnancy is an immunodeficient state may well be a consequence of the outdated paradigm that some degree of immune paralysis of the mother was required to protect the fetal allograft against immune attack. Biased observers therefore tended to find what they expected to find when looking for clinical sequelae of this presumed immunodeficiency. Our current concepts recognise that fetal trophoblast is not susceptible to attack by T cells but suggest that other aspects of the immune system may be modulated during pregnancy as part of a series of maternal adaptations necessary for successful fetal development. Current evidence does not suggest any clinical consequences, but—as always—we must recognise that our knowledge remains partial and in need of continual review.

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Open all hours: night visits in general practice

A new twilight service is meant to reduce the load

Home visiting is enshrined in the terms and conditions of service of general practitioners in the NHS, who are required to visit patients in their own homes if in their opinion the patient's condition demands it. Home visits have increased fivefold over the past 25 years, with a substantial increase in night calls since the introduction of the 1990 contract.¹ Last year, night visits in England cost the NHS £70 million.² Protests from distressed general practitioners have reached a crescendo, with most being baffled by the lack of underlying clinical explanation for this increase in their workload. Many general practitioners have also shown quite clearly that they no longer want to be available to their patients at all times and would happily trade independent contractor status for a salaried service to be rid of out of hours work.³

Negotiations between the General Medical Services Committee on behalf of general practitioners and the minister for health have come up with interesting solutions that will have implications for home visiting in general.⁴ Doctors will in future have more discretion about whether to visit—this decision will be based on the doctor's reasonable opinion. Such a reasonable opinion will be based on information supplied in most cases in a telephone conversation between doctor and patient or the patient's representative. Studies have shown that general practitioners can deal with a high proportion of night calls by telephone,⁵⁻⁷ but it is acknowledged that consulting over the telephone is diagnostically more difficult.⁸ Presumably if the doctor does his or her best at eliciting a history and then decides not to visit, this qualifies as a reasonable opinion, at least to the doctor, his or her peers, and hopefully to a service committee.

Of course, patients may not see it that way. As one patient remarked, "I would like to be satisfied that his decision to go back to sleep is professional rather than merely human,"⁹ reflecting a widely held view that returning to sleep after a telephone interruption is a matter of turning over. Doctors may well need a record of such consultations to show that they have made reasonable attempts at eliciting the history. The charge of "failure to visit" is one of the most common reasons for general practitioners appearing before a service committee.

Experiments with alternative methods of supplying medical care out of hours have focused on pilot primary care emergency centres. In the short term, use of such centres has led to a fall in out of hours calls, but we do not know if this is a true fall in demand for out of hours visits or merely the result of rationing. For some people—for example, the increasing minority who find it difficult to get to their doctor during conventional surgery hours—such centres may well meet an

unmet need for medical care. Primary care emergency centres are set up not for this purpose but to provide emergency medical care at night. Most accident and emergency departments believe that providing non-urgent care out of hours is what they do anyway, and they complain loudly about it. They will now have an opportunity to reroute some patients back to an emergency centre. Such action may reduce overall demand on accident and emergency departments and may ultimately keep patients out of hospital, further reducing costs.

Are these centres to act only on referral? If a strict referral policy is not applied then patients are likely to approach these centres directly. Patients will gradually see them as providing a 24 hour service rather than an emergency service. The centres will of necessity be located in the more densely urbanised areas and will need to be supported by doctors who can also make visits to patients' homes, otherwise an emergency ambulance service will be needed. Such centres will need to be staffed by doctors because of the clinical skills demanded by emergency medicine. Practice nurses have so far kept well away from medicine outside daylight hours.

At present the public have a 24 hour general practitioner service for a pittance. It is just as likely that the increasing cost of the out of hours service, still a pittance, is as powerful an impetus for the recent changes as the obvious distress of general practitioners. The root cause, patient demand, is still a mystery, and providing yet another service, a twilight service, will not deal with the problem. Indeed it may well add to it. The government and the profession need to keep talking while continuing to educate patients about the proper use of their general practitioner at night.

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