



## Tudors, Tolerance, and Pregnancy Loss

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Recurrent pregnancy loss is an unfortunate fact of life for many women. This special issue of the *Biomedical Journal* includes four review articles from renowned experts discussing the factors important for a successful pregnancy and, in particular, the complex immunological dialog between mother and fetus. We also focus on an animal study investigating the utility of skin-derived hydrogels for wound healing, unearth the details of a rare stomach cancer, and discover new applications for silver in dentistry. (*Biomed J* 2015;38:1-4)

**Key words: fetal–maternal tolerance, hydrogels, recurrent pregnancy loss, wound healing**

### SPOTLIGHT ON REVIEWS – Tudors, Tolerance and Pregnancy Loss

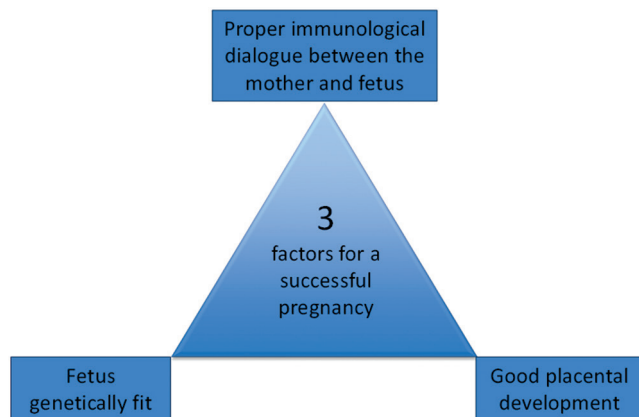
At the height of Tudor England, Anne Boleyn, the second wife of King Henry VIII, suffered a series of miscarriages that contributed to the loss of her influence, and eventually her life, for failing to produce an heir to the throne. Unfortunately, Anne's plight is not uncommon, with an estimated 1–5% of women experiencing recurrent pregnancy loss (RPL). This special edition of the *Biomedical Journal* includes four review articles from experts across the world examining the genetics of RPL and the mechanisms important for maternal–fetal tolerance.

First, Daniel Vaiman describes the genetics behind miscarriage.<sup>[1]</sup> Unsurprisingly, the situation is complex, with a wide variety of factors determining whether a pregnancy is successfully carried to term or spontaneously aborted. These factors include the genetic integrity of the fetus, levels of oxidative stress in the placenta, and immunological dialog between the mother and fetus [Figure 1]. Many single nucleotide polymorphisms leading to the dysfunction or abnormalities in the expression of genes involved in these pathways are associated with RPL in humans.

Of particular importance is the key component

of the immune system's surveillance program, the major histocompatibility complex (MHC) aka human leukocyte antigens (HLA), which present self and non-self peptides at the cell surface for inspection. As Dr. Vaiman points out, compatibility of HLA antigens between the mother and fetus is a key determinant of pregnancy success, with high homozygosity in the mother leading to an increased risk of pregnancy disorders,<sup>[2]</sup> presumably because the chance of allele sharing with the father is low.

To limit T cell responses against the semi-allogenic fetus, trophoblast cells at the fetal–maternal interface do not express MHC class II molecules. However, these cells do express MHC class I molecules, including HLA-G, which is the subject of a review by Philippe Le Bouteiller.<sup>[3]</sup> HLA-G exists in both membrane-bound and soluble forms and is a specific ligand of many cellular receptors present on maternal cells. Thus, HLA-G not only induces apoptosis of activated CD8 + T cells by stimulating the Fas/FasL pathway,<sup>[4]</sup> but also influences many other immune cells, including CD4 + T cells, natural killer (NK) cells, macrophages, and dendritic cells (DCs). Remarkably, this multi-functioning molecule also influences placental development by regulating the secretion



**Figure 1:** A successful pregnancy depends on three main factors: The genetic integrity of the fetus, good placental development, and proper immunological dialog between the mother and fetus. Idea for figure suggested by Dr. Ludivine Doridot.

of angiogenic factors.<sup>[5]</sup> Thus, HLA-G acts like a guardian toward the fetus, ensuring protection from the maternal immune system and facilitating placental development which is essential for fetal growth.

Continuing with the theme of maternal–fetal tolerance, Bracamonte-Baran and Burlingham discuss how the developing fetal immune system tolerates non-inherited maternal antigens (NIMA),<sup>[6]</sup> defined as the specific alleles of polymorphic genes expressed by the mother but not the fetus. Microchimerism appears to play an important role in tolerance. During pregnancy, the trophoblast allows the bidirectional trafficking of stem cells and immune cells, giving rise to a small number of maternal cells in fetal tissues and vice versa.<sup>[7]</sup> Based on their findings and those of other studies, the authors propose a model in which maternal cells take up residence in fetal organs and generate exosomes containing NIMA on their surface. These exosomes are taken up by DCs resulting in a subpopulation expressing allogeneic maternal antigens and induce the subsequent reprogramming of these cells, turning them from immunogenic to tolerogenic DCs.

Finally, Tripathi and Guleria discuss the regulation of maternal–fetal tolerance by Th17 and Treg cells,<sup>[8]</sup> which prevent uncontrolled immune responses. The authors also examine the role of the programmed cell death 1/programmed cell death 1 ligand (PD1/PDL1) pathway, which controls the conversion of Th1 cells to a Treg phenotype and may stimulate the differentiation of the uncommitted helper T cells into paternal antigen-specific Treg cells.<sup>[9]</sup>

Overall, these reviews provide an extensive summary of the constellation of interactions that are important for fetal–maternal tolerance, which explain how a genetically distinct organism can develop within the mother. Hopefully, this knowledge will lead to the development of new therapies that may see RPL consigned to history books.

## SPOTLIGHT ON ORIGINAL ARTICLES – Can Skin-based Hydrogels Help to Heal Wounds?

The human body has a remarkable capacity for repair following trauma. Nonetheless, poor wound healing remains a significant clinical challenge and modern medicine has little support to offer. In this issue of the *Biomedical Journal*, researchers from the Chang Gung Memorial Hospital investigate whether hydrogels derived from skin can facilitate wound healing.<sup>[10]</sup>

Treat damaged skin with skin. The idea itself seems simple and forms the basis for skin graft operations. In this case, Cheng and his team focused on a particular part of skin, the basement membrane (BM), which plays an important role in normal skin physiology and wound healing. Epithelial cells sit on top of this fibrous section of extracellular material, and its degradation and resynthesis is a rate limiting step in wound closure. The supply of biomaterials mimicking extracellular matrix is thought to enhance healing, so what can be a better starting material than the BM itself?

Cheng and colleagues previously developed a novel method for generating extracellular matrix (ECM)-rich, tissue-derived hydrogels from various source tissues and showed that those derived from dermal tissue contain BM proteins including laminins and collagens essential for proper skin function.<sup>[11,12]</sup> Applying this technique, they derived hydrogels from dermal extracts of rat skin and determined the functional properties of the resultant hydrogels by atomic force electroscopy. Satisfied with the results, the team then applied the hydrogels to the surface of wounds made to the back skin of rats and compared wound healing over the course of several weeks using rats receiving no treatment as a control.

The authors examined the extent of angiogenesis by CD31 immunolabeling and quantified histological variables including the size of the unclosed wound and the quantity of granulation tissue. The hydrogels did not promote inflammation and tended to limit the formation of granulation tissue. However, the gels had completely disappeared by 1 week and overall there was no significant difference in wound healing between hydrogel-treated and control rats.

Chen puts this finding down to the poor stability of the gels, as dermal-derived hydrogels have shown promise for skin regeneration in other studies.<sup>[13]</sup> The challenge thus is to make them more stable, for example, by covalent cross-linking. This should hopefully enable the essential BM proteins and growth factors that they contain to take effect, thus providing the skin with a helping hand from a familiar set of molecules.

## ALSO IN THIS ISSUE: NEWS

The Tang Prize was created by Dr. Yen Liang Yin in 2012 with the aim of encouraging attempts to tackle global issues such as climate change and inequality. The foundation is proud to announce that the winners of the 2014 Tang Prize in Biopharmaceutical Science are Prof. James P. Allison and Prof. Tasuku Honjo for the discovery of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) as immune inhibitory molecules which has led to their application in cancer immunotherapy.<sup>[14]</sup>

### ORIGINAL ARTICLES – Measuring Bite after Mandibular Reconstructive Surgery with the T scan System

The T scan system is a diagnostic device that records the force and dynamics of a patient's bite. Liu *et al.*<sup>[15]</sup> report the first study to investigate post-rehabilitation occlusal function with the T scan III system in patients with a reconstructed mandible. They conclude that occlusal force is not an appropriate measure for assessing prosthetic function.

### Details of Rare Stomach Cancer Revealed

In this retrospective study, Lin and colleagues<sup>[16]</sup> search through hospital records to identify patients with a rare but deadly cancer, gastric hepatoid adenocarcinoma. Their study provides the much needed information about this little known disease, including demographic characteristics of patients, their biological variables, treatment regimens, physical appearance of the disease on endoscopy, and survival rate. Unfortunately, prognosis is poor, but patients may survive longer with chemotherapy.

### Reawakening of Dormant Viruses May be Bad News for Critically ill Individuals

Most of us host one or more viral invaders, such as herpes virus, cytomegalovirus, and Epstein-Barr virus (EBV). Thanks to our immune system, we are mostly unaware of their presence, but the reactivation of these viruses can cause problems in immunodeficient individuals. Libert *et al.*<sup>[17]</sup> reasoned that serious illness may also provide a breach leading to the activation of these viruses in otherwise immunocompetent individuals. They found that EBV is reactivated in over two-thirds of patients admitted to the ICU for more than 5 days and showed that this event may signal a poor outcome for the patient.

### Silver Smile? Growth of Oral Bacteria Halted by Precious Metal

When damage to the dental root occurs, dental pulp, the living tissue within teeth, is often surgically replaced with mineral trioxide aggregate (MTA). However, MTA has no antibacterial activity, leaving the tooth susceptible to infection during the procedure. Here, Bahador and colleagues<sup>[18]</sup> investigate the antibacterial activity of MTA containing nanoparticles of silver (NanoAg), which can prevent the growth of bacteria. Their *in vitro* findings show that NanoAg-MTA limits the growth of several common oral pathogens and may be a beneficial additive for root canal repairs.

### Measuring Athletic Performance by Mathematics

Heart rate is frequently used by coaches and fitness trainers as a measure of performance. In this report, Nikolaidis tests two commonly used equations to assess the maximal heart rate of athletes according to their age and proposes a new sport-specific equation for soccer players.<sup>[19]</sup>

### Integrated Training Improves the Communication Skills of Medical Professionals

Being a good doctor requires not only an extensive knowledge of medicine but also excellent interpersonal skills. Chen and Chou examined a slightly unusual method of medical education, an integrated training program, whereby participants were taught how to lead guided tours of Taiwan Medical Museum, and found that this program improved the communication skills of medical students.<sup>[20]</sup>

### LETTER – Comment on Article by Kapil and Bhadoria

In a recent issue of the *Biomedical Journal*, Kapil and Bhadoria reported an association between television viewing and obesity in children.<sup>[21]</sup> In a comment on this article, Tanuj Kanchan points out that other electronic gadgets,<sup>[22]</sup> such as mobiles, tablets, iPads, gaming consoles, and laptops, that have somewhat replaced television viewing in the 21<sup>st</sup> century, also need to be taken into consideration. In their reply,<sup>[23]</sup> Kapil and Bhadoria agree that the lack of physical activity associated with all these devices is indeed an important risk factor for obesity, although television itself may actually lead to an increase of energy intake through snacking or motivation to consume junk food from advertisements.

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