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EDITED AND REVIEWED BY
Lucienne Chatenoud,
Université Paris Cité,
France

*CORRESPONDENCE
Surendra Sharma
ssharma@wihri.org

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Editorial: The placenta, fetomaternal tolerance and beyond: A tribute to Sir Peter Medawar on the 60th anniversary of his Nobel Prize

Gabriela Barrientos¹, Maria Emilia Solano²,
Sandra M. Blois³ and Surendra Sharma^{4*}

¹Laboratorio de Medicina Experimental, Hospital Alemán. Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Ciudad Autónoma de Buenos Aires, Argentina, ²Laboratory for Translational Perinatology- Focus: Immunology, University Department of Obstetrics and Gynecology, University Hospital Regensburg, Regensburg, Germany, ³Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, ⁴Department of Pediatrics, Women and Infants Hospital-Warren Alpert Medical School of Brown University, Providence, RI, United States

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Editorial on the Research Topic

The placenta, fetomaternal tolerance and beyond: A tribute to Sir Peter Medawar on the 60th anniversary of his Nobel Prize

Sir Peter Medawar era and beyond

Sir Peter Medawar revolutionized our knowledge about how a semi-allograft fetus can evade maternal immune system (Figure 1) (1). Although the old concepts of tissue transplantation as he considered them may not entirely apply to our current understanding of fetal immune tolerance, his Nobel Prize winning ideas provided us a platform to build on the new paradigms to understand the intricately choreographed orchestration of immunity at the maternal-fetal interface. The pregnant uterus is amply replete with immune cells which theoretically should reject the fetus. However, non-cytotoxic cross talk between specialized uterine immune cells and the placenta is thought to be a critical factor in maintaining local immune tolerance. On the other hand, among the vulnerable populations, pregnant women and their fetuses have traditionally represented a high-risk population during viral pandemics and in response to stress factors and intrauterine microbial infections in general. These events are likely to induce altered maternal immunity and effect on gametogenesis and organogenesis as well as placental functions. Adverse pregnancy outcomes are on the rise globally and to date, no clear

mechanistic underpinnings or therapeutic options are available. Importantly, long-term effects of *in utero* exposure to viral or bacterial products and of severe pregnancy complications are still not known. A question that also remains unaddressed is whether *ex-vivo* recapitulation is possible to understand the pregnancy continuum involving inflammation-associated implantation through the anti-inflammatory phase of pregnancy and inflammation-associated parturition.

This Research Topic on the placenta and fetomaternal tolerance during pregnancy centers around consequences for Normal Pregnancy and Maternal and Neonatal Health and presents cutting edge information on various aspects of basic systemic and uterine immunity, placenta as a regulatory and infectious target, and clinical observations in pregnant women. The articles included in this collection provide knowledge that assimilates the current understanding and goes beyond the Medawar era. We hope this issue will be of benefit to researchers globally, interested in the role

of cutting-edge concepts that have been put forward to unravel mechanisms that underlie pregnancy complications.

Urgent need for contemporary and comprehensive information on maternal tolerance in pregnant women

Over the years, there has been an explosion of publications on fetomaternal immune tolerance in general, including those reporting on clinical consequences for pregnant women. However, the information to the general public has suffered from fragmented reports and data derived from mice and humans sometimes not corroborating. Clinical evaluation of the mechanisms derived from animal models has been very

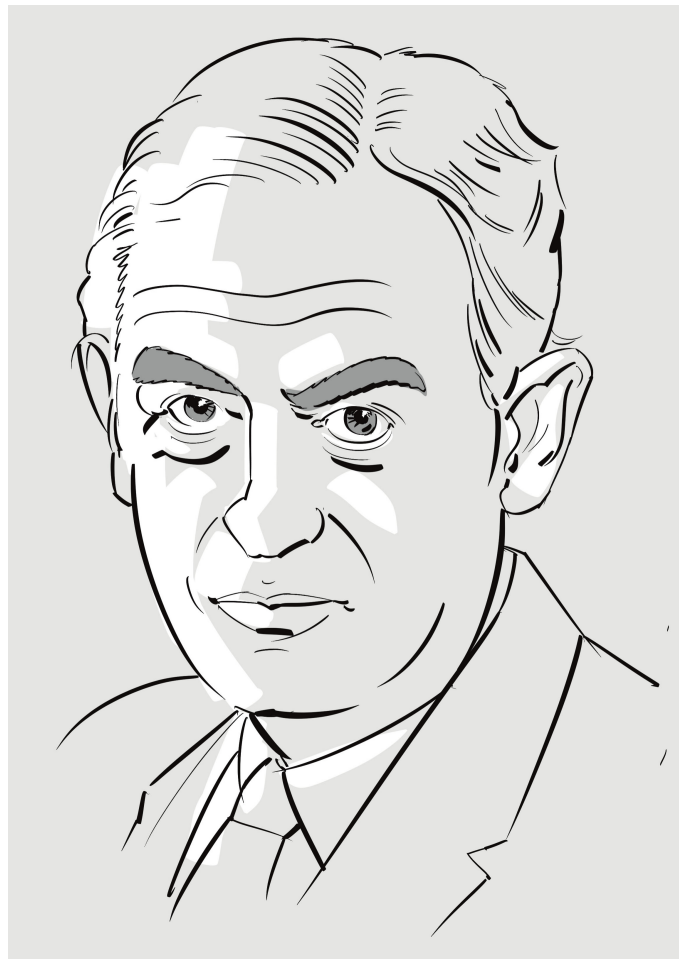


FIGURE 1
Sir Peter Medawar: 1915-1987 and Beyond.

helpful but still needs validation from human models. In this context, state of the art technologies such as whole genome sequencing and single-cell proteomics provide invaluable tools to gain insight into the immunological landscape throughout the pregnancy continuum, from the **embryo-endometrial crosstalk** driving implantation and **aberrant immune interactions** in preeclampsia, to the signals promoting the **onset of labor** and the **maturation of the immune** system in preterm born infants as illustrated by original research featured in this collection. The twenty-three manuscripts comprised in this Research Topic cover most of the cutting-edge information on important issues relating to pregnancy, immune cells, placenta, cytokines, hormones, extracellular vesicles, and neonatal health. Each review or original article is authored by experts on the specific topic of their respective research and/or clinical work.

Infections, immunology and consequences

The uniqueness of the uterine mucosal lining relies in that it provides a nurturing environment to the fetal allograft while at the same time remaining competent to mount an effective immune response towards infections. Articles within this Research Topic also addressed the mechanisms involved in the **uterine response against viral infections**, including observational studies reporting an **inefficient placental infection by SARS-CoV-2** and poor manifestation of maternal and neonatal immune responses. These observations relate to the question whether pregnancy contributes to controlled or severe COVID-19 disease. Unlike other coronaviruses, SARS-CoV-2 infected pregnant women remain asymptomatic with rare incidence of mortality. Also, even in the post Medawar era, the question as to how maternal immune cells are educated to support pregnancy and the identity of the signals triggering immune rejection remain major challenges. Novel findings on **antigen presenting cells**, maternal **HLA Ib polymorphisms**, allorecognition by **uterine NK cells** and **type 1 CD8+ T cells** shed light into these important questions. On the other hand, new observations suggest that certain immune cells, for example **mucosal-associated invariant T cells**, and **bacterial components**, albeit with low abundance, may function as anti-microbial defense and support pregnancy development, respectively. This Research Topic also includes important contributions of **cytokines**, **carbohydrate Lewis antigens**, glycan binding proteins, **adhesion molecules**, **HLA-DR antigens**, and **placental inflammasome** in programming a continuum of pregnancy complications including preeclampsia, **gestational diabetes mellitus**, fetal growth restriction and preterm birth.

Clinical consequences of aberrant uterine immunity on maternal and neonatal health

Several manuscripts have been devoted to review the current data and conceptualize the various factors integral to the understanding of diagnostic challenges, therapeutic controversies, intrauterine transmission, and maternal and neonatal complications. Among these, contributions on **CD8+ T cells** and **decidual NK cells** provide an updated perspective on immune cell biology at the maternal fetal interface and the impact on health and disease. Together with articles illustrating current knowledge on **glycoimmune interactions**, **immunosuppressive signatures** expressed by placentally derived extracellular vesicles and **their synergy with microchimeric cells**, we have curated a comprehensive outline of the intricate mechanisms governing fetomaternal tolerance covering the entire gestation period from disease severity, management considerations for care of severe and critically ill women, role of co-infections, and prenatal care and labor.

We hope that manuscripts included in this Research Topic will provide cutting edge insights for diverse aspects of placental microenvironment in pregnant women and its effects on maternal and neonatal health.

Author contributions

SS conceptualized the work, SS and GB drafted the first version. SB designed the illustrations included in this work. All authors contributed to the final version and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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