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Demystifying Animal Models of Adverse Pregnancy Outcomes: touching bench and bedside

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Introduction

This represents an overview, and not an exhaustive (or systematic literature) review of the use of animal models to study the adverse pregnancy outcomes seen in humans. For several of the outcomes mentioned herein there exist more in-depth reviews and there likely will be more to follow. Nor is this a review of all the data and mechanisms relating to normal and abnormal pregnancy and parturition. I have decided to include a balance between older reports and observations and reviews by revered scientists, as well as newer observations and reviews by seasoned and perhaps less-seasoned investigators. My hope is that clinicians will be able to utilize some of this information to seek out the literature and have more meaningful and profitable discussions with their academic colleagues. I further hope that they will be enticed to engage in regular interactions that will enhance transdisciplinary research in reproductive health. My ultimate agenda is to eliminate the tendency to dismiss work in animal models out of hand because they don't exactly capture human physiology. In addition, I want to prevent the thinking that little can be learned from observations in humans because of inability to modulate and study specific mechanisms. I would like to see more support for conversations starting from both sides with "This is how I understand how the model behaves and how it might (or not) be reflected in humans. What is your understanding?" I would also like to see the literature, including titles of manuscripts and key words increase visibility of the animal models (e.g. including the words "animal model" and species name) involved in the observations conveyed.

Why animal models?

The limitations of human studies to establish disease causality and of in vivo animal models to replicate human physiology support the use of animal models in an iterative manner. In this process, phenomena described following observational studies in humans drives hypotheses to be tested in animal experiments. Animal experimentation in turn refines hypotheses that can then be tested in humans. This in turn leads to further questions and more productive animal experimentation. In this iterative approach, studies in humans and animals complement each other and can synergize to move our understanding of disease forward. That being said, my bias is that a good animal is not meant to primarily replicate all of what happens in humans, nor is it meant to be *directly transferable*. A well-working model generates logical and testable hypotheses that are consistent first foremost with existing data in the animal, and possibly in humans as well. The drive for those who

primarily use animal models should be to “know thy model”, be able to communicate it effectively to others, and to generate productive integrative and iterative study.

An approach to animal models

In studies in humans, several properties are taken into consideration to determine the appropriateness of the group of patients accessed for a study. These properties may be related to certain demographics or to prevalence of disease. When considering animal models to study adverse pregnancy outcomes, several issues come to mind.

Resources

With decreasing funding through federal and other sources, cost may play a large role in the choice of mode. Larger animal models are likely more costly and research based on these models is receiving less support[1]. However, certain strains of genetically manipulated mice are also very expensive (http://jaxmice.jax.org). The animal welfare regulatory requirements for non-human primate work are increasingly stringent as is the administrative oversight. Another constraint is the ability to deal with the public relations issues necessary to utilize primate models. Only certain institutions have the capacity, specialized facilities and highly-trained veterinary staff. Depending on the species, there are some zoonotic disease issues which require a very rigorous occupational health program. Another practical issue related to choice of animal models is the presence of experts working with that model. Just as it is often better to watch a relative cooking a family tradition, rather than relying on a recipe, there are likely to be small bits of “inside” or not widely published information about the model that are more easily obtained by direct contact with the investigator utilizing the model.

Placentation

Current thinking would refute the notion that the placenta is just a passive membrane between mother and fetus. Early studies of nutrient uptake suggest that most of the resources delivered to the uterus are utilized by this organ. The placenta is selfish. It is a metabolically hormonally, and immunologically active entity in a triune necessary for successful pregnancy: mother, fetus, placenta. Structurally, the purpose of the placenta in mammals is to bring maternal and fetal circulatory systems in close proximity to facilitate exchange of nutrients, oxygen, waste and other factors[2]. Several good reviews of comparative placentation exist[3–7]. Placentae are usually described by the layers existing between fetal trophoblast, which itself envelops fetal vessels and mesenchymal cells, and maternal blood[2]. The controversy of placentation and the validity of animal models will likely continue because while it is assumed that differences in placentation will lead to different adaptive mechanisms, experimental changing of placentation in certain animals is likely extremely challenging.

The human placenta is said to be hemochorial[2], in that maternal blood is in direct contact with fetal trohpblast. There are however, other points of contact between maternal and fetal tissues, for example in the villous structures that anchor the placenta[8]. The human placenta moreover is said to be interstitial, in that implantation occurs completely within the maternal

uterine wall[4] thus allowing for multiple points of interaction between maternal and fetal tissues early in gestation. Primates commonly used in research, e.g. baboons, macaque, chimpanzee also have hemochorial placentas[3, 6] with more or less invasion upon implantation, and a villous organization, although this is not true for all primates (e.g. lemurs[3]). The vascular structure of human placenta undergoes a revision in early gestation in which trophblast lines maternal uterine arteries[9] to allow for maximal blood flow[10]. The placenta in rats (see recent review by Soares[11]) mice and guinea pigs (rodents) is similar to that in humans in that maternal blood is in direct contact with trophoblast. There are subtle(?) structural differences between human and rodent placentae, including the flow of blood due to a labyrinthine as opposed to a villous organization, the depth of trophoblast invasion[6], and the trophoblast subpopulations[2]. For example, an additional layer of trophoblast, the giant cell layer, in addition to cytotrophoblast and syncytital trophoblast has led some authors to call the rodent placenta “hemotrichorial”. Because of only one trophoblast layer, the guinea pig placenta is sometimes referred to as “hemomonochorial”. In addition to structural differences, there are subtle differences in the expression of proteins, such as those involved in immune regulation[12–15]. While the definitive placenta is in place for a short time relative to gestation in mice and rats[2], the longer gestation in guinea pigs makes this less true. Rabbits belong to the group of mammals called lagomorphs. Their placentas are hemochorial with two trophoblast layers, a syncytium and a cytotrophoblast layer which is similar to humans, but organized in a labyrinthine structure[2, 5, 16]. Sheep and pigs belong to the group of mammals called ruminants (order Artiodactyla) and have a different placental structure where both trophoblast and uterine epithelium are intact but interdigitate (epitheliochorial, think fingers of folded hands) allowing for contact close enough for efficient gas exchange[2]. In some areas of the sheep placenta, called placentomes there is aggressive interdigitation between trophoblast villi on the fetal side (cotyledon) and the uterus on the maternal side (caruncle) and at points the epithelia form a common syncytium allowing for more efficiency of gas and nutrient exchange. Pigs have a similar but more diffuse placental structure than sheep with less aggressive interdigitation[217].

Uterine structure, dynamics

The human/primate uterus is a single muscular organ different structurally from the two-horned uterus of rodents (for mice see Margaret J Cook’s book at www.jax.org), pigs[18], rabbits[16] or sheep[19]. While the electro-mechanics of the human/primate uterus may be fundamentally different from that seen in other species[20, 21], the uteri of rodents[22], rabbits[23] sheep[24] and pigs[18] respond to oxytocin, suggesting a common expression of the receptor and most have been used to study the mechanisms underlying uterine contractility in vitro.

Endocrinology of pregnancy

In addition to hormones such as estrogen (discussed elsewhere), progesterone is a key hormone of pregnancy that appears to be differentially regulated in humans and animals[25]. The particulars of the responsiveness to this hormone and its interaction with estrogen in successful pregnancy remain a topic of intense investigation. In humans, the corpus luteum is the major site of progesterone expression with help from chorionic gonadotropin released by the early conceptus[26]. Blockade of progesterone during this time causes pregnancy loss[26]. Major production of progesterone switches to the placenta by 5–6 weeks gestation.

Maternal serum levels of progesterone raise post conceptionally and continue to elevate beyond parturition[25, 27]. However, progesterone has been given with variable success with to treat women with recurrent miscarriage[28] and anti-progesterone given late in pregnancy can cause cervical ripening and delivery in some women[29] suggesting a complex biology.

Human fetal membranes can produce[30] and metabolize progesterone[31], and locally produced progesterone metabolites may be important in uterine quiescence and activation[32]. The human uterus can produce an inhibitory progesterone receptor which increases before parturition[33]. Finally, progesterone receptor regulation at multiple levels in the cytoplasm and the nucleus may regulate functional progesterone activity leading to parturition[34]. Progesterone's regulation during pregnancy in related non-human primates is similar to human pregnancy in several respects including dependence on early production of progesterone by the corpus luteum[35], that early pregnancy can be interrupted by antiprogestins[36] and that there is not systemic withdrawal before parturition[37].

In rodents, the corpus luteum is the source of progesterone that maintains pregnancy. Luteolysis[38], removal of the ovaries[39], or administration of antiprogestational agents[40] leads to uterine activation with increased effective signaling through oxytocin or other receptors and parturition. The difference in serum levels before parturition in mice and rats is said to make these animal a poor model for progesterone regulation in humans. However, further understanding of local progesterone metabolism and responsiveness is likely to reveal mechanisms that are to some extent important in humans and may be a natural stand in for women who do not respond to exogenous progesterone in the prevention of preterm birth. Rats also express an inhibitory receptor that increases in expression before parturition[41].

In guinea pigs, in which early pregnancy can be disrupted by antiprogestins[42], maternal serum levels, similar to what is seen in humans, rises from the time of conception to a peak in early gestation followed by a transient decrease in late gestation and increasing levels from that point beyond the time of parturition[25]. Rabbits and sheep in contrast have very low levels of progesterone in the serum as compared to humans, and in these animals, pregnancy brings a slight increase in serum progesterone and a rapid fall before parturition[25].

Another important endocrine system related to pregnancy is the hypothalamic pituitary adrenal axis[43], both of the mother and the fetus. Activation of the HPA axis by stress or other factors initiates a cascade involving release of corticotropin releasing hormone (CRH) from the hypothalamus, secretion of corticotropin (ACTH) from the anterior pituitary, and action of ACTH on the adrenal to release cortisol and other glucocorticoids which can then exert feedback suppression on their release. This system not only interacts with the immune system, but is also thought to be part of the mechanism underlying poor pregnancy outcomes related to emotional or physiologic stress[4445]. CRH, a principle mediator of the HPA axis is produced by the placenta and fetal membranes[45], and may be a mediator of local estrogen production. In pregnant women, the possibility for multiple sources of increased systemic CRH presents an ongoing challenge in understanding the interaction between maternal stress, fetal stress and normal HPA development in the generation of parturition or preterm birth[46]. Animal models are likely critical in the examination of this issue in that they can be

used to isolate and understand the potential importance of maternal versus fetal HPA, and other factors[47, 48] in this process.

In related non-human primates, the placenta also expresses CRH, and development of the fetal adrenal and activation of the fetal HPA axis generate important support signals for normal labor[48]. Compared to humans, the biochemistry of adrenal steroid production and the development of the fetal adrenal gland in various non-human primates show subtle differences that may need to be considered in choosing a primate model to examine the role of the HPA axis in normal development or prematurity[49].

In rats and mice the HPA axis expresses important differences from that found in humans. For example, the major product of HPA axis activation in humans is cortisol, while that in most rodents it is corticosterone[50]. Moreover, the development of the fetal adrenal gland in rats and mice is markedly different with major relative deficiencies in important enzymes and preference for different substrates. In these species, the response to stress may lead to fundamentally different means of pregnancy failure, including a decreased level of circulating progesterone[51]. While rodent models may not be ideal for examination of the role of the HPA axis in normal pregnancy, evolving rodent models may be of interest in understanding the interaction of the HPA axis and stress in parental behavior[52].

Sheep have been used as a model of maternal[53] and fetal HPA axis function during pregnancy. In this animal model, it is the development and activation of the fetal HPA that is the primary driver of parturition[54], and stresses such as hypoxia activate the HPA axis in sheep and lead to preterm labor[55]

Immune system

The maternal-fetal interface in humans includes not only close contact between maternal and fetal cells within the placenta and uterus[8] but also within the maternal and fetal circulations, as cellular traffic has been shown in either direction[56, 57]. The expression of proteins unique to the mother on fetal cells has raised a decades-long debate over the critical pathways and mechanisms needed to assure both immune tolerance and protection of the fetus from infection[58]. Humans can mount an immune response against fetal antigens during pregnancy[59], and it is clear that there is an intricate interaction between maternal immune cells and trophoblast[60, 61]. This interaction may be of benefit to the evolving conceptus[62] or may be involved in early pregnancy loss or other adverse pregnancy outcomes[63]. Activation of local innate immunity within the myometrium is thought to play a role in parturition[64], and in premature uterine contractions[65]. In humans, certain pathogens are more deleterious during pregnancy as compared to the non pregnant state[66] while others are not[67] and the role of the placenta as a safe harbor for evolving pathogens has been described[68]. Some infection syndromes that occur in humans occur only under contrived conditions in animals[69]. Moreover, some organisms, such as CMV are different in different hosts[70]. Both the peculiarities of the immune response and the infectious agent must be taken into consideration when using an animal model to understand the function of the immune response during pregnancy.

The maternal- fetal interface in primates expresses similar oligomorphic Major Histocompatibility (MHC) molecules[71] and other immune modulating factors[48] as are found in humans. Similar populations of immune cells have also been observed in the primate uterus and placenta during pregnancy[72–74]. Moreover, shared susceptibility to certain infections exists[75]. In addition, the high degree of sequence similarity between key human and non-human primate protein sequences has supported the use of anti-human antibodies in ELISA and other immune assays to examine the immune response in non-human primates. These factors have made primate models useful for the study of infection, immunity and adverse pregnancy outcome.

Mice have also been used extensively to model both maternal innate and adaptive immunity. There has been extensive study on the trafficking of cells across the maternal-fetal interface[76–78] and on the intricate interaction between trophoblast and innate immune cells in gestation[79, 80]. While there are some differences in the phenotype of natural killer (NK) cells at the maternal-fetal interface[81], and differences in the diversity of the MHC molecules expressed on trophoblast subpopulations in humans and mice[82], both systems have been used to delineate specific mechanisms and paint a picture of NK cells as “educable”[83, 84], supportive of placental structure and development[82], but potentially participating in disruption of pregnancy[85] (and see below).

The mouse has also been used to examine maternal T cell regulation during pregnancy. As in the human, the pregnant mouse can generate a fetus specific immune response[77], including effector and regulatory T cells[86, 87]. An advantage to the mouse is the ability to vary the genetic difference between mother and fetus. For example, some strains of mice respond to the male antigen, H-Y, and thus maternal immunity can be studied in a situation where mother and fetus are genetically identical, except for the expression of proteins relevant to maleness. The so- called anti H-Y response is generated in mouse pregnancy[77], and has been shown to shown modulate both CD4[88] and CD8[89] maternal T cells. Several genetically modified antigen systems have been used to examine maternal anti fetal immunity in pregnant mice[90]. Although human but not mouse T cells can present antigen via MHC II, the mouse has also been used to examine fetal antigen presenting cells during pregnancy[91, 92]. Integrated studies in mice and humans will likely increase our knowledge of the function of the immune system during pregnancy and reveal the presence and importance of specific pathways.

Guinea pigs and humans have similar immune systems making them a useful tool in the study of relevant human infectious diseases[93]. Guinea pigs are extensively used in models of anaphylaxis and allergy[94]. Many tools are now available to examine the immune system in these animals[95].

The rabbit has also been used for a variety of immunology and infectious disease research. The whole genome of the rabbit has been sequenced and utilized to determine possible genomic differences in loci responsible for immunity[96].

As in humans and mice, systemic immunity during pregnancy has been examined in sheep. Some studies have found no alteration during pregnancy[97] while other studies have found

the sheep produces pregnancy-specific agents that can suppress immune responses[98]. In human pregnancy, there is a systemic turnover of a subtype of T cells, bearing gamma and delta chain T cell receptor in the peripheral blood[99]. These gamma-delta T cells are also present in the deciduas[100] and may play a role in fetal protection[101]. A highly diverse population of gamma delta T cells is present in sheep uterus during pregnancy, providing large numbers of cells for study[102, 103]. Pigs have also been studied to understand immunity at the maternal- fetal interface, and for example underlined the importance of uterine NK cells[104].

Length of gestation and fetal development

In human and other primate gestation, implantation is ~ 7–8 days after ovulation followed by a 10 week long pre-embryonic and embryonic period[28]. This is followed by a prolonged fetal period resulting in a highly developed fetus in relatively low numbers. During this time multiple insults inside and outside the uterus can disrupt both pregnancy and fetal well being. For ease of experimentation, a shorter length of gestation, such as found in most rodents (i.e. ~ 19–22 days) may be desired. However, the rodent fetus is born less developed than the human[105]. Currently, tissue-specific inducible promoters, Cre-recombinase and related technology allow for the generation of genetically-based time and tissue-specific modulation of gene expression during mouse pregnancy. These changes can be examined in the developing fetus and the newborn. However this technology may be difficult to obtain, and mice with the desired modifications may not exist. Moreover, the short gestation and small fetal size constrain the ability to make specific surgical or physiologic interventions and relate these to fetal development. While rats are relatively larger, and more amenable to these interventions, the technology to generate targeted gene expression or deletion in rats is less-developed or utilized[106].

The guinea pig is a rodent used in many studies of maternal environment and fetal development, as it has a longer gestation of 68 days[2], and its offspring are born highly precocious[105] with a mature central nervous system at birth[105]. Another rodent with a longer gestation is the “spiny mouse” of the genus *Acomys* (not *Mus* as in mice). This small rodent has a relatively long gestation (38–42 days) and gives birth to a small litter (2–3 pups) that are born highly developed[107]. These exotic animals however are difficult to manage due to their delicate skin[108]. There is a long and distinguished history using rabbits to understand early development[16] In rabbits, ovulation is induced by mating, resulting in an exactly defined pregnancy and embryonic age assessment. Larger animals, such as sheep, have long and lower order gestations (singleton/twin) and produce highly developed offspring and thus have been used for studies of pregnancy insult on fetal development[109].

Preeclampsia

Preeclampsia is a pregnancy-related syndrome that affects multiple systems and clinically presents as hypertension, proteinuria, edema and in its more sever forms evidence of fetal compromise, neurologic abnormality, liver and hematologic dysfunction[110]. The complexity of the syndrome defies the development of a panel of genetic screens or biomarkers[111]. While the basic cause of the disease is as yet unknown, multiple hypotheses exist. These include failure of placentation[112] and thus reduced utero-placental perfusion, intolerance to

volume expansion generated by pregnancy[113], infection[114] and inflammation[115]. It is hotly debated as to whether failed placentation is caused or a by-product of broken maternal immune tolerance[116, 117]. Many agree that a common final pathway to the manifestation of the disease is endothelial cell damage occurring in a variety of vascular beds[118].

While the disease is thought of as being uniquely human, many recognize the potential positive role of integration of research in human and animal models in understanding the underlying mechanisms[119, 120]. The hallmarks of preeclampsia most sought after in animal models are hypertension, renal dysfunction (proteinuria), and further, conditions such as poor trophoblast invasion and endothelial damage. Current models address some of these issues.

There have been rare reports of spontaneous preeclampsia in related non-human primates[121]. These species have also been used to develop models of pregnancy-related hypertension and proteinuria based on injection during mid- gestation of inflammatory mediators, such as Tumor Necrosis Factor[122] or antibodies to interleukin 10[123].

There are strains of mice that spontaneously develop hypertension, proteinuria, smaller litters and fetal demise and these have been used to model preeclampsia[124, 125]. There are also models of spontaneous pregnancy-associated hypertension with fetal compromise in rats[126]. There also exist genetically manipulated mouse and rat models. In one interesting genetic model of hypertension in pregnancy, female mice transgenic for human angiotensinogen are mated to males transgenic for human rennin[127]. The resulting pregnancy is marked by distortion of placental anatomy, elevation of circulation Vascular Endothelial Growth Factor (VEGF) receptor in mid gestation (12–13 of 19–20 days), hypertension, fetal intrauterine growth retardation and systemic maternal disorders including proteinuria and convulsion. In the rat version of this model[128] the hypertensive disease experienced by the pregnant rat is thought related to secretion of rennin from the placenta into the maternal circulation[129]. Interestingly, the extent of trophoblast invasion into the spiral arteries in these pregnancies was increased compared with non pregnant animals, and the breeding, when done in reverse (dams transgenic for rennin males for angiontensinogen) was associated with lower blood pressure. Overall studies in humans, in vitro, and in animal models have yielded interesting hypotheses surrounding the placenta as a independent factor in the development of preeclampsia. Animal models, in conjunction with genetic studies in humans[113] will likely elucidate an important underlying mechanism(s) for the disease.

To model the presumed decrease in placental perfusion that occurs as part of the mechanism proposed to incite preeclampsia[130], workers have ligated various levels of the uterine artery. The RUPP or reduced uterine perfusion pressure model (reviewed in[131]) is performed in rats and several other animals. In rats the model is performed at around 14 days of gestation by placing a clip above the aortic bifurcation and on both sides of the uterine arcade to prevent utero-ovarian collateral flow. This results in a 40% or more reduction in flow to the developing fetal-placental units, and the resulting disease includes hypertension, renal damage (proteniuria), increased vascular reactivity and small pups. In rats an alternative of this model is based on increased salt intake and administration of desoxycorticosterone acetate[132], which generates hypertension, convulsions, proteinuria and renal lesions[133].

Other rodent models of reduced vascular function have utilized injection of inhibitors of nitric oxide (i.e. L-NAME (N-omega-nitro-l-arginine methyl ester[134]), or over expression of soluble VEGF receptor (sVEGFRI, sFLT1) or members of the Transforming Growth Factor β receptor complex (i.e. endoglin). Adenovirus–driven over expression of sFLT1 in pregnant rats leads to hypertension and proteinuria in a dose-dependent manner[135], and this is enhanced by over expression of soluble endoglin[136].

Other animals have also been used to develop models of preeclampsia. In guinea pigs there have been reports of a naturally occurring preeclampsia-like syndrome[137]. In addition, it has been observed that banding of the uterine arteries as well as transaction of the ovarian arteries before pregnancy results in later pregnancy hypertension, proteinuria and elevated creatinine[138]. Moreover, early observations of constriction of the aorta in pregnant rabbits revealed that such manipulation generated hypertension, proteinuria, weight gain, and reduced weight of the fetus[139]. Finally, sheep experience what is call toxemia of pregnancy, that appears to be a very different metabolic disorder as compared to preeclampsia[140], but does include proteinuria and inflammation[141].

Intrauterine growth restriction

In humans, intrauterine growth restriction (IUGR) can be an independent outcome of a fetal abnormality or related to placental insufficiency due to a number of maternal/environmental factors including poor nutrition, smoking and chronic infection, or in the context of preeclampsia[142]. Poor intrauterine growth has been extensively studied in animals[143], and thus the time is ripe for more extensive integration of the information in humans and animals.

In related primates, IUGR has been induced using various levels of maternal nutrient restriction[144], and surgical manipulation of placental blood supply[145] among other interventions. In animals with litters, there is evidence that the fetuses placed at a distance from the main uterine artery are smaller[146]. In pigs, a proportion of piglets in a litter is naturally small[146, 147].

In mice, genetic models of deficiency in key molecules such as eNOS have been generated and pups of these pregnancies show IUGR[148] while their mothers do not show a characteristic mid-gestation drop in systemic blood pressure[149]. In mice and rats bilateral uterine artery ligation late in gestation leads to fetal intrauterine growth retardation, neurologic deficiency and metabolic derangement[150]. Uterine artery ligation at mid gestation (~day 30 of 70) in guinea pigs also produces growth restriction[151].

Ligation of utero-placental vessels in rabbits on day 25 of a 31 day gestation produces small pups that show deficiencies in neurobehavioral development[152]. Administration of L-NAME on day 24–28 of gestation is also used to model IUGR in a rabbits and this model results in growth retarded fetuses and decreased flow, as determined by 3D power Doppler Angiography, in each utero-placental unit[153].

In sheep, there are several models of fetal growth restriction[109]. These include maternal calorie restriction[154] emobilization of the umbilico-placental arteries[155], and disruption of

the uterine epithelium in close contact with trophoblast in the placenta[156]. Maternal hyperthermia gestation day 35–40/~147 gestation[157–159] has been shown to produce asymmetrical growth restriction and decreased placental mass, and abnormal umbilical arterial and aortic Doppler velocimetry[160], while placement of the mother in hypoxic conditions also limits fetal growth[161]. Some breeds of sheep are more amenable to these manipulations than others[109], suggesting that with advanced technology and genome sequencing, these animals may be used to examine gene-gene- and gene-environment interaction in the development of this disease.

Recurrent miscarriage

Human pregnancy is less efficient than many other species, as nearly 50% of conceptions fail[28]. In humans, recurrent miscarriage is a complex syndrome that likely incorporates several types of defects in genetics, implantation, placentation, metabolism, and hormonal support of the conceptus[28, 162] or stress[163]. Thoroughbred horses[164] and commercial pork breeds[165] also have a high rate of spontaneous abortion. One idea that drives the field is that disregulation of maternal innate or adaptive immunity initiates or contributes significantly to the disease[166, 167]. Immune modulation as a treatment in human disease has met with variable success, and this is still a matter of controversy[168]. Whether an initial metabolic, structural or related defect leads to immune activation and a subsequent deleterious response or an initial loss of immune regulation leads directly to tissue disregulation and destruction is still a matter of debate in some circles. Thus, the issue of immune-mediated recurrent pregnancy loss is one that is likely amenable to iterative studies in animal models and humans.

In primates, parental sharing of MHC has been correlated with decreased pregnancy success[169]. Moreover, administration of anti-progestational agents can produce early pregnancy loss, as in humans[170]. Primates have also been used to develop models of pregnancy loss related to infections[171].

A well-known mouse model of pregnancy loss involves the breeding of a CBA strain female mouse with a male DBA strain male. Depending on the source and housing (level of pathogens present) of the mice, pregnancies can be affected by high levels of fetal-placental degeneration (referred to as “resorption”)[172] and infiltration with NK and other immune cells[173]. In this model, resorption of the fetuses occurs at approximately day 9–12 of gestation[174]. Contributors to increased fetal loss in this model include stress[175], inflammation[176, 177] abnormal cytokine milieu within the placenta/decidua[178, 179], disrupted regulatory immune modulation[180, 181] and abnormal placental vascular development[182, 183]. Several methods of immune modulation[184–187] have been shown to decrease fetal loss in this model, but few if any have been successfully translated to clinical care[28]. More recent models of pregnancy loss in mice involves chemically targeting[86] depletion[87] or genetic deficiency of a subpopulation[188] of regulatory T cells in normal C57Bl/6 females mated to same strain or allogeneic males. An alternative immune- based models of pregnancy loss involved NK T cell activation in certain strains of mice[189], and systemic immune activation leading to ovarian insufficiency[190].

Study of the high rate of pregnancy loss in commercial pork breeds has further suggested the role of immune cells in supporting successful pregnancy[191]. Moreover, Guinea pigs (for example[192]) and Sheep[193] have been used in models of early pregnancy loss in response to infection. Finally, autoimmune related loss, as in the antiphospholipid syndrome has been modeled in rabbits[194].

Preterm birth/prematurity

The study of premature birth presents at least three major issues that are amenable to studies in animal models[195]. The first is the discovery of mechanisms leading to premature labor. A second pertains to delineating consequences of being born premature. Thirdly, animal models have been employed to devise ways to better manage the premature neonate. While the factors contributing to prematurity in humans are far from understood, emerging data suggests that preterm births fall into definable categories[196]. These categories include preterm births in women who have a history of preterm birth[197], in women with multiple gestations[198], women who are undergoing an infectious or inflammatory process[199–201], women who undergo social and emotional stress[202], and women who have medically indicated or physician-driven premature births[203]. While in general, animals are not said to experience preterm birth, there is variability in gestation within species. Recent data for example, suggests that there is significant variability in mouse gestation related to strain[204] or cytokine expression[205].

Endocrine disruption

Progesterone has been used in various formats for the prevention of preterm birth[206, 207]. Clearly, there are patients who respond to progesterone, and those who do not. Only a proportion of women respond to vaginal progesterone, particularly if the cervix in shortened. Even amongst women with a tendency towards preterm birth as evidenced by a previous premature delivery, there are those who respond to regular administration of a progestational agent while others do not. Finally, with the reinstatement of progesterone and related agents in the past decade, there remains a significant incidence of preterm birth[208]. Use of animal models in conjunction with a more careful study of responders versus non responders[209] in human trials of progesterone and related agents will enhance our understanding and management of pregnancy.

Decreased relative progesterone activity can be modeled in mice via oophorectomy or administration of agents such as RU486 in primates (see above). Preterm birth can also be generated in rabbits using RU486[210]. Novel models of endocrine disruption in mice[211]and likely other animals are being developed. In several animal models, a signal from the fetus, the placenta, or the endometrium leads directly or indirectly through a systemic response circuit to decreased relative progesterone activity and increased estrogen activity[212, 213]. This in turn leads to increased prostaglandin (increased production, decreased hydrolysis), uterine contractions, cervical ripening and subsequent rupture of membranes and expulsion of the fetus. For example, the stress response, thought to be mediated by cortisol is modeled in sheep by systemic administration of glucocorticoid[214] or in the fetus[215]. The complexity of these models is likely to increase, and bring forth possible means to modify the process of disrupted endocrine function in premature birth[34].

Immune/inflammatory In very well studied models in mice (for examples[216–218]), rabbits[219220, 221]and primates[222–224] exposure of the uterus to an inflammatory signal or infectious process leads to an increased local presence of inflammatory cells[218, 225] and feeds into the mechanisms resulting in increased uterine contractions or cervical ripening and subsequent preterm birth. An interesting alternative inflammatory model involves injection of a major lung surfactant protein which is thought to activate uterine macrophages and lead to preterm birth[213]. Guinea pig uterus is particularly sensitive to mast cell secreted mediators, making this a potentially important model for examining the role of allergy an preterm birth[226227].

A salient example of the iterative nature of successful research in animals and humans is the work surrounding Toll-like receptors and preterm birth. In the early 1960s, it was recognized that urinary tract infections in women were associated with preterm birth[228, 229]. The 1970's brought forth reports that lippopysaccharide, a component of the outer membrane of gram negative bacteria interrupts early and late pregnancy in mice[230] and rats[231]. In 1985, the *Toll* gene in Drosophila was cloned[232]. The early 90's brought studies suggesting that LPS-induced preterm delivery induced changes in local and systemic cytokines including tumor necrosis factor-alpha and interleukins 1,6, and 8[233, 234]. In the late 90's, the drosophila *Toll* gene was linked to antifungal immunity and the delineation of the Toll-like receptor (TLR) family of proteins began[235–237]. At this time it was recognized that a certain strain of mice was hypo-responsive to LPS[238]. That these mice possessed mutations in the *Tlr*4 locus generated much excitement that *Tlr*4 was the innate receptor for LPS and the link between infection and LPS-mediated inflammation. The early 2000s brought studies trying to link polymorphisms in *Tlr4* to LPS responsiveness, preterm labor, and preterm premature rupture of membranes in humans[239]. In the mid-late 2000s, investigators using mouse models determined that preterm delivery induced by bacteria expressing LPS is dependent on TLR4 signaling.[240] They delineated several relevant pathway constituents, including Myeloid Differentiation primary-response gene 88 (MyD88)[241], nuclear factor kappa B(NFκB)[242] cytokines, such as tumor necrosis factor and others[243] and prostaglandins[244]. At about this time began studies of expression and regulation of these molecules and their pathways in human placenta, uterus and decidua[245, 246] and the correlation between *Tlr4* expression and other adverse pregnancy outcomes in humans[115, 247]. Recently, a TLR4 antagonist was tested in a rhesus model for decreasing LPS-induced inflammation and uterine contractions[223]. Moreover, the role of other TLR molecules in preterm birth[248–250] has generated experiments linking bacterial and viral co-infection with preterm birth[251], suggesting synergy in signaling from two TLRs. Finally, data are developing that link circulating fetal DNA and yet other TLRS with this process[252].

Important complications of prematurity in humans that are investigated in animal models include white-mater damage and cerebral hemorrhage which is thought to be the basis for cerebral palsy and learning disability[253]. Studies of preterm birth in humans have supported the idea that not only infection but also inflammation is a significant underlying cause of preterm birth[254]. In addition, this data has contributed to the idea that the fetus generates a significant inflammatory response under these conditions[255] and that this response may subject the fetal brain to processes leading to cerebral palsy[256]. Several animal models have

been used to examine fetal neurologic insult in the context of maternal systemic infection or inflammation and the resulting preterm labor. These studies have included systemic injection of LPS in pregnant sheep[257] and intrauterine injection in rabbits[258] and in mice[259–261]. The mouse model of preterm birth initiated with injection of LPS revealed the important role of the cytokine interleukin 10[262, 263]. In addition, human studies have suggested the potential role of this cytokine in modifying preterm birth related brain injury[264]. The study of inflammation-related preterm birth and brain injury offers another opportunity for productive iterative study in humans and animals.

Adverse fetal programming

"Programming" is said to occur during "a critical period when the system is plastic and sensitive to the environment followed by loss of plasticity and a fixed functional capacity"[265]. "Fetal programming" in humans is said to occur as a result of adaptation to undernutrition in an adverse intrauterine environment contributes significantly to obesity, metabolic syndrome, and cardiovascular disease[266]. Increasingly, animal models are being used to delineate these mechanisms, and several models utilizing rats, mice, rabbits sheep, and nonhuman primates have been utilized (see Fischer[16], Seki[267], and Vuguin[158] for reviews)]. Some of these models proceed through well recognized defects in fetal development, such as IUGR. This issue is one that is ripe for an iterative process involving studies in animals and humans. An area that would be particularly amenable to animal experimentation would be the examination of multigenerational effects of exposure during pregnancy[268].

Is the future now? Bioinformatics and the iterative use of animal models

Although the relevant tissue in humans is sometime hard to access, genetic variability found from sampling peripheral blood can be informative in conjunction with specific gene manipulation in rodents. For example, technology exists to manipulate embryos by using viral constructs to target genes to trophoblast[11, 269]. It is therefore not difficult to imagine an experimental paradigm whereby candidate genes from human genetic studies would be considered for over expression or "knock down" in trophoblast using this technology. Pregnancies using these manipulated embryos could then be observed or further challenged and observed for preterm birth. In this way, and perhaps many others, bioinformatics, systems biology and the use of animal models could be woven into and increasingly efficient iterative method to understand the complex biology of abnormal pregnancy.

The overwhelming increase in genomic, transcriptomic, proteomic, metabolomic, and now microbiomic data in human disease requires continued development of methodologies to probe and understand existing data. Once understood, however, specific genes/proteins reveal themselves as important and these can then be analyzed in animal models[270]. Similarly, "omic" data from animal models can theoretically be used to query existing repositories from human studies[271].

Finally, the large amount of data in both humans and animal will further advance our ability to mathematically model pregnancy[272] and perform *in silico* experiments and use machine

learning[273]. The time may come when the iterative method I propose between human studies and animal models may require this third facet in the quest to understand reproduction.

Post note

This shallow overview was meant to increase curiosity and enhance discussion between clinicians and researchers who utilize animal models in the study of adverse reproductive outcomes. The solution to these problems will come from an integrative and iterative method that starts from clear identification of studies in animals in the literature, an enhanced understanding of the available models and the increased willingness to see value in what at first may seem obscure.

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