Response to a Call for Papers from World Health Organization

Health in the Post-2015 Development Agenda

Measurement of Progress towards the Health Goals:

What are the best Indicators and Targets for Health?

"Recommendation: Preeclampsia should be included as an Indicator for improving Maternal Health and reducing Child Mortality, Millennium Development Goal 4 and Goal 5"

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On behalf of

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Introduction/Abstract[3]

For years scientists have tried to understand the "immunological paradox" which pregnancy inevitably presents. Normally, the human body naturally tends to reject cells with foreign DNA. However, in a healthy pregnancy, the woman's body generally does not attack but rather, accommodates the foreign cells of the embryo she has conceived.[4] On the other hand, in the case of preeclampsia, the pregnant woman's body rejects the embryo she has conceived due to an "immunologic intolerance between maternal and fetal tissue."[5] Research shows that the etiology of preeclampsia (a major cause of maternal mortality, pre-natal infant mortality and pediatric complications in the Developing World) is causally related to the lack of uterine "seminal priming."

The Etiology of Preeclampsia and the Role of Seminal Priming

Why are some women prone to life-threatening preeclampsia?[6] According to immunologists, the answer involves the role of semen in sustaining a healthy pregnancy. The working hypothesis among many immunologists is that maternal T-cells, her so-called immunological border guards,[7] are first "primed" by repeated deposits of seminal fluid during

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[3] The content of this paper will included in an article in the upcoming edition of the *Ave Maria Law Review*, Volume 11, Issue 2 (Spring 2013).

[4] Martin, A, "Microchimerism in the Mother(land): Blurring the Borders of Body and Nation" *Body and Society*, vol. 16 no. 3, 2010, 35 citing Lee J. Nelson (2001) "The Chimeric Self- Cellular Traffic between Mother and Fetus Raises Questions about the Causes of Autoimmune Disease," Natural History 110 (5):14-16; also see Galofre, JC, "Microchimerism in Graves' disease," J of Thyroid Research (2012) 2.

[5] Saftlas, A., Levine, R., Klebanoff, M., Martz, K, Ewell, M., Morris, C., Sibai, B, "Abortion, Changed Paternity, and Risk of Preeclampsia in Nulliparous Women," *Am J. of Epidemiology*, Vol. 157, No. 12, 2003, 1109 citing El-Roeiy A, Gleicher N. The Immunologic concept of preeclampsia, In: Rubin PC, ed. Handbook of hypertension. Vol 10. Amsterdam, Netherlands: Elsevier Science, 1998:257.

[6] "Preeclampsia, characterized by sustained hypertension with proteinuria occurring after 20 weeks' gestation and spontaneous resolution after delivery, is one of the most common pregnancy disorders and a leading cause of maternal mortality. The consequences of preeclampsia also include preterm delivery and intrauterine growth retardation, resulting in high perinatal morality." Li DK, Wi S. "Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy," *Am J Epideminol* 2000;151:57-62, 57.

[7] Martin, A, "Microchimerism in the Mother(land): Blurring the Borders of Body and Nation" *Body and Society*,

sexual intercourse with the same man:

> [I]nsemination is hypothesized to constitute a 'priming' event, acting to induce maternal immune tolerance to paternal transplantation antigens, many of which are present in semen and shared by the conceptus.[8]

These genetically-specific male antigens located in semen reprogram the maternal T-cell lymphocytes[9] to accept cells with this particular antigen, which would normally be rejected by the mother's immune system as foreign invader cells. However, due to this seminal priming, maternal lymphocytes treat the embryo, which present the same antigen-identification as found in the semen, as native cells:

> Semen may contribute to the induction of immunological tolerance towards paternal transplantation antigens, thereby favoring the survival of the semi-allogenic conceptus.[10]

Consequently, in a successful pregnancy, the maternal T-cell lymphocytes actively assist the conceptus exhibiting the same antigen-presenting cells previously encountered in the semen, rather than arresting and attacking them as foreign invaders:

> [E]xposure of the female reproductive tract to seminal TGFβ [transforming growth factor beta] initiates an influx of antigen-presenting cells that sample ejaculate antigens and subsequently activate lymphocyte populations in lymph nodes draining the uterus…TGFβ is implicated as a potent immune deviating agent in the uterus. Thus, the processing of paternal transplantation antigens in a milieu containing high levels of TGFβ of seminal plasma origin may result in the generation of hypo-responsiveness in paternal antigen-specific T-lymphocytes. It is reasonable to postulate that, upon re-encounter with the conceptus antigens, these regulator or effector T-cells might contribute to an immunological

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vol. 16 no. 3, 2010, 36.

[8] Robertson, SA, Sharkey, DJ, "The role of semen in induction of maternal immune tolerance to pregnancy," *Seminars in Immunology*, vol. 13, 2001: 243-254, 243.

[9] Robertson, S., Bromfield, JJ, Tremellen, KP, "Seminal 'priming' for protection from pre-eclampsia – a unifying hypothesis," *J. of Reprod. Immun*. (2003) 253-265, 255.

[10] Kelton P. Tremellen, Diana Valbuena, Jose Landeras, Agustin Ballesteros, Javier Martinez, Sergio Meddoza, Robert J. Norman, Sarah A. Robertson and Carlos Simon, "The Effect of Intercourse on Pregnancy Rates during Assisted human Reproduction," *Human Reproduction Oxford Journals* (2000) 15 (12): 2653-2658, 2658 citing Roberston, S.A., Mau, V.J. and Tremellen, K.P. "Cytokine-leukocyte networks and the establishment of pregnancy." Am. *J. Reprod. Immunol.* (1997), 37, 438-422.

environment favoring successful implantation and optimal placental growth.[11]

This "tolerogenic" (suppressed) immune response produced by seminal antigens was first noted in mice.[12] Additional animal studies confirmed that it was semen—and not the physical act of copulation—that initiated the "inflammatory cascade" of immunologic tolerance that consequently improved litter size.[13] Providing further confirmation of the indispensable role of seminal fluid, women with high rates of miscarriage were also shown to experience significant improvement with embryo implantation after using seminal plasma pessaries was applied.[14] Also, women exposed to the semen of their male partners though sexual intercourse showed significantly higher rates of viable embryos at six to eight weeks of gestation after embryo transfer following in vitro fertilization.[15]

However, this tolerogenic priming effect on a woman's immune system, allowing for improvement in embryo implantation rates, appears to be lost if she changes male partners. Because preeclampsia seems to be caused by an overly aggressive maternal immune response towards paternal antigens detected in the embryo,[16] researchers argue that the genesis of this pathology is linked to a woman's immunological memory of particularized antigens in male semen: "[T]he observations of partner specificity and cumulative benefit of semen exposure imply that immunological 'memory' of partner's antigens may be programmed at

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[11] Robertson, S., Bromfield, JJ, Tremellen, KP, "Seminal 'priming' for protection from pre-eclampsia – a unifying hypothesis," *J. of Reprod. Immun*. (2003) 253-265, 261-262.
[12] Ibid., 258 citing Lengerova A., Vojtiskova, M., "Prolonged survival of syngenic male skin grafts inparous C57 B1 mice, *Folia Biol.* (1966) 8, 21-25.
[13] Tremellen, K.P., Robertson, S.A., "Seminal 'Priming' for Successful Mammalian Pregnancy," Chapter 9, *Reproductive Immu*nology, S.K. Gupta (Ed) (new Delhi, India, Narosa Publishing House, 1999), 88-97, 89.
[14] Kelton P. Tremellen, Diana Valbuena, Jose Landeras, Agustin Ballesteros, Javier Martinez, Sergio Meddoza, Robert J. Norman, Sarah A. Robertson and Carlos Simon, "The Effect of Intercourse on Pregnancy Rates during Assisted Human Reproduction," Human Reproduction Oxford Journals (2000) 15 (12): 2653-2658, 2658 citing Coulam, C.B. and Stern, J.J. (1995) Effect of seminal plasma on implantation rates. *Early Pregnancy*, 1, 33-36.
[15] Ibid., 2658.
[16] Ibid.

insemination."[17]

Studies show that when a woman's immune system is not primed and has no immunological memory of particularized antigens in male semen due to withdrawal or barrier method contraceptives, those embryos that are conceived frequently fail to implant. One study demonstrated that "single women who used barrier contraception had a 2-fold higher risk of developing preeclampsia."[18] Researchers at Chapel Hill, North Carolina Memorial Hospital, conducted an unconditional logistic regression analysis that indicated a 2.37-fold (95% confidence interval, 1.01 to 5.58) increased risk of preeclampsia for users of contraceptives that prevent exposure to male ejaculate.[19] In another study, a 2.4-fold increased risk of preeclampsia was concluded for users of contraceptive methods that inhibit interaction with male semen.[20] Yet another study found a 2.52-fold (with 95% confidence interval, 1.17 to 5.44, $p < 0.05$) increased risk of preeclampsia for users of barrier contraceptives compared with women using non-barrier contraceptive methods.[21]

Other researchers have demonstrated "that prevalence of preeclampsia in primigravida women is associated with weekly number of coitus before conception and the use of barrier contraceptive methods."[22] Dr. Jon Einarsson, an obstetrician/gynecologist at Baylor College of medicine in Houston, Texas, reporting to the American College of Obstetricians and Gynecologists (ACOG) on his recent study, noted the following:

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[17] Robertson, S., Bromfield, JJ, Tremellen, KP, "Seminal 'priming' for protection from pre-eclampsia – a unifying hypothesis," *J. of Reprod. Immun*. (2003) 253-265, 255.

[18] Davis, J, Gallup, G, Preeclampsia and other pregnancy complication as an adaptive response to unfamiliar semen. Chapter 10 in *Female Infidelity and Paternal Uncertainty: Evolutionary Perspectives on Male Anti-Cuckoldry Tactics*, ed. Steven M. Platek (Cambridge Univ. Press, 2006), 191-204, 194.

[19] Klonoff-Cohen HS, Savitz DA, Celfalo RC, McCann MF, *JAMA*, 1989, abstract.

[20] Dekker, GA, "The Immunological Aspects of Preeclampsia: Links with Current Concepts on Etiology and Patholgenesis," Chapter 3, *Hypertension in Pregnancy* (New York, Marcel Dekker, Inc., 2003) 4.

[21] Hernandez-Valencia M, Saldana Quezada L, Alverez Munoz M, Valdez Marinez E. "Barrier family planning methods as risk factor which predisposes to preeclampsia," *Ginecol Obstet Mex.* 2000 Aug;68:33-8, abstract.

[22] Bastami, P, Hamdi, K, Abdollahi A, "Preconception Period of Seminal Fluid Exposure and Prevalence of Preeclampsia in Primigravida Women," *J. Med. Sci*., 7 (5): 840-844, July 1, 2007, abstract, 840.

> Women who use barrier methods who had been having sex with their partners for less than 4 months prior to getting pregnant had a 6.5-fold increased risk of getting preeclampsia, compared with women who did not use barrier methods and had been in a sexual relationship for more than 12 months.[23]

Hence, the question arises: why does a woman's body react as it does to seminal priming? Some researchers speculate that both the size of the human brain (compared to other mammals) and the amount of nutrient that is devoted to its development in the second and third trimesters (up to 60%) require "a second wave of implantation."[24] It seems that "[t]he large size of the human brain requires deep endovascular trophoblast invasion[,]"[25] which constitutes the second and more involved implantation not found in other mammals. Prior exposure to the same male antigens found in the embryo is critical to the success of this second phase of implantation:

> [H]umans are the only species to undergo a second phase of implantation, there may be a critical period of prenatal development in which the presence of the father's semen facilitates the second phase of implantation.[26]

In sum, "[e]xposure to paternal alloantigen occurs in two waves in the reproductive process—initially during transmission of seminal fluid at coitus, and secondly when placental trophoblast cells invade maternal tissues during embryo implantation."[27] In other words, paternal antigens are presented to the woman's immune system in two procreative waves: first, by the semen and second, by the embryo itself, should fertilization occur.

Although the complete etiology of preeclampsia still remains largely a mystery to the medical community, immunologists are certain that seminal fluid priming significantly improves

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[23] Excerpt by Jacqueline Stenson, Reuter's Health, PreventDisease.com, http://preventdisease.com/news/articles/condoms-preeclampsia.shtml, last visited 12/26/12.

[24] Davis, J, Gallup, G, Preeclampsia and other pregnancy complication as an adaptive response to unfamiliar semen. Chapter 10 in *Female Infidelity and Paternal Uncertainty: Evolutionary Perspectives on Male Anti-Cuckoldry Tactics*, ed. Steven M. Platek (Cambridge Univ. Press, 2006), 191.

[25] Dekker, GA, "The Immunological Aspects of Preeclampsia: Links with Current Concepts on Etiology and Pathogenesis," Chapter 3, *Hypertension in Pregnancy* (New York, Marcel Dekker, Inc., 2003) 49-50.

[26] Davis, J, Gallup, G, Preeclampsia and other pregnancy complication as an adaptive response to unfamiliar semen. Chapter 10 in *Female Infidelity and Paternal Uncertainty: Evolutionary Perspectives on Male Anti-Cuckoldry Tactics*, ed. Steven M. Platek (Cambridge Univ. Press, 2006), 191-204, 198.

[27] Robertson, SA, Guerin, LR, Moldenhauer, LM, Hayball, JD, "Activating T regulatory cells for tolerance in early pregnancy – the contribution of seminal fluid" *J. of Reprod. Immunology*, 83 (2009) 109-116, 112.

the odds of avoiding this disease.[28] This working hypothesis is corroborated by evidence that a previous pregnancy fathered by the same man reduces the rate of preeclampsia.[29] In this way, a previous normal pregnancy provides protection against preeclampsia,[30] provided that the second pregnancy is fathered by the same man who fathered the first.[31] This holds true even when the first pregnancy is terminated by an elective abortion:

> Women with a history of abortion who conceived again with the same partner had nearly half the risk of preeclampsia…In contrast, women with an abortion history who conceived with a new partner had the same risk of preeclampsia as women without a history of abortion. Thus, the protective effect of a prior abortion operated only among women who conceived again with the same partner.[32]

Preeclampsia Affects Maternal Health and Child Mortality in the Developing World

Preeclampsia is one of the three leading causes of maternal morbidity and mortality in the world.[33] 2% to 8% of all pregnancies are complicated by preeclampsia.[34] Preeclampsia and eclampsia account for 10% to 15% of all direct maternal deaths.[35] The relation between preeclampsia and eclampsia is explained as follows:

> Preeclampsia and eclampsia are not distinct disorders but the manifestation of the spectrum of clinical symptoms of the same condition. The mildest disorder in this continuum is pregnancy-induced hypertension. In preeclampsia, hypertension and proteinuria are present, and when convulsions occur in addition to these signs, the

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[28] Li DK, Wi S. Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy. *Am J Epidemiology* 2000; 151:57.
[29] Koelman, C.A., Coumans, A.B., Nijman, H.W., et al. (2000). Correlation between oral sex and low incidences of preeclampsia: a role for soluble HLA in seminal fluid? *Journal of Reprod. Immunology*, 46, 155-166, 156.
[30] Ibid., citing Strickland, D.M., 1986, "The relationship between abortion in the first pregnancy and development of pregnancy-induced hypertension in the subsequent pregnancy." *Am J. Obstet. Gynecol. Reprod. Biol*. 61, 85-87.
[31] Li DK, Wi S. Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy. *Am J Epidemiology* 2000; 151:57-62, 61.
[32] Saftlas, A., Levine, R., Klebanoff, M., Martz, K, Ewell, M., Morris, C., Sibai, B, "Abortion, Changed Paternity, and Risk of Preeclampsia in Nulliparous Women," *Am J. of Epidemiology*, Vol. 157, No. 12, 2003, abstract.
[33] Ghulmiyyan L., Sibai B., "Maternal mortality from preeclampsia/eclampsia," *Seminars in Perinatology*. 1012 Feb:36(1):56-9, abstract.
[34] Duley, Lelia, "The Global Impact of Pre-eclampsia and Eclampsia," *Seminars in Perinatology* 33:130-137, 2009, abstract.
[35] Ibid.

condition is referred to as eclampsia.[36]

Not only is preeclampsia a leading cause of maternal mortality, but it has also become a leading cause of prenatal infant mortality.[37] As is only to be expected, the global impact of preeclampsia is felt most severely in the developing world where its prevalence ranges from 1.8% to 16.7% of all pregnancies[38] due to the inadequacy of primary health care:

> Preeclampsia has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally. However, the impact of the disease is felt more severely in developing countries, where, unlike other more prevalent causes of maternal mortality (such as hemorrhage and sepsis), medical interventions may be ineffective due to late presentation of cases. The problem is confounded by the continuing mystery of the etiology and the unpredictable nature of the disease.[39]

The World Health Organization (WHO) has taken note of the serious threat preeclampsia and eclampsia pose to both mothers and their infants:

> Hypertensive disorders of pregnancy are an important cause of severe acute morbidity, long-term disability and death among mothers and babies.[40]

> In Africa and Asia, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy, whereas one quarter of maternal deaths in Latin America have been associated with those complications. Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity.[41]

WHO makes the following recommendations to lower the incidences of pre-eclampsia in the Developing World: reduce physical activity, reduce dietary salt intake, increase calcium intake if low, take low-dose aspirin, take antihypertensive drugs, take magnesium sulfate, induce

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[36] Kayode O. Osungbade and Olusimbo K. Ige, "Public Health Perspectives of Preeclampsia in Developing Countries: Implication for Health System Strengthening" Journal of Pregnancy, vol. 2011, Article ID 481095, 1.
[37] Davis, J.A., and Gallup, G, *Female Infidelity and Paternal Uncertainty: Evolutionary Perspectives on Male Anti-Cuckoldry Tactics*, (Cambridge University Press, 2006) Chapter 10 "Preeclampsia and other pregnancy complications as an adaptive response to unfamiliar semen," 191.
[38] Kayode O. Osungbade and Olusimbo K. Ige, "Public Health Perspectives of Preeclampsia in Developing Countries: Implication for Health System Strengthening" Journal of Pregnancy, vol. 2011, Article ID 481095, abstract.
[39] Ibid., 1.
[40] World Health Organization, "Who recommendations for Prevention and treatment of pre-eclampsia and eclampsia," (2011) *WHO Press*, NLM classification: WQ 215, 4.
[41] Ibid., 1.

labor if a mother is pregnant with a non-viable fetus or if the fetus is unlikely to achieve viability within one or two weeks (constituting an elective abortion) and engage in expectant therapy (wait and see) in cases where the fetus is viable, otherwise induce labor.[42] WHO puts great emphasis on the relatively inexpensive drug, magnesium sulfate, in the management of pre-eclampsia and eclampsia.[43]

Researchers suggest that in order to reach Millennium Development Goal 5 (improving maternal health), "preeclampsia needs to be identified as a priority area in reducing maternal mortality in developing countries."[44] The Preeclampsia Foundation, working in consultation with the USAID, states that reaching Millennium Development Goal 4 (reducing child mortality) and Millennium Development Goal 5 (reducing maternal mortality) will depend largely on comprehensive and innovative programs to address preeclampsia and eclampsia.[45]

Conclusion and Recommendations

Globally, approximately a half a million women die in childbirth annually with 99% of these deaths occurring in the developing world,[46] most of which are preventable.[47] Progress towards improving maternal health, MDG 5, is "further off-track than any of the other MDGs."[48] In order to get MDG 5 back on track, the United Nations needs to include preeclampsia as an indicator for assessing progress in reaching this goal as well as MDG 4.

In addition to its evidence-informed policy that magnesium sulfate should be used to treat

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[42] Ibid., 8-26.
[43] Ibid., 30.
[44] Kayode O. Osungbade and Olusimbo K. Ige, "Public Health Perspectives of Preeclampsia in Developing Countries: Implication for Health System Strengthening" Journal of Pregnancy, vol. 2011, Article ID 481095, 4.
[45] Preeclampsia Foundation, "Most maternal deaths from preeclampsia are preventable," *The News*, last updated on September 14, 2012, www.preeclampsia.ag/the-news/3-newsflash/243-preclampsia-toolkit-released-for-developing-countries.
[46] Falconer, Anthony, "Millennium Goal 5," Obstetrics, Gynecology and Reproductive Medicine 20:12, p. 369.
[47] Ibid.
[48] Ibid., 371.

preeclampsia, WHO should also recommend the avoidance of barrier method contraceptives as best practice to prevent the onset of preeclampsia, especially in cases of first pregnancy. For WHO to fail to warn women about the evidence linking barrier method contraceptives to a 200%-650% increase in the incidences of preeclampsia would be to neglect the charge given to all UN agencies by the Human Rights Council to consider "all relevant factors in order to accelerate the realization of the rights of women and girls and the achievement of Millennium Development Goal 5 by 2015."[49]

Wherefore the Society of Catholic Social Scientists and International Solidarity and Human Rights Institute strongly recommends that preeclampsia should be included as an Indicator for improving Maternal Health and reducing Child Mortality, Millennium Development Goal 5 and Goal 4.

[49] United Nations Human Rights Council, twenty-first session, Agenda item 3 (21 September 2012) "Preventable maternal mortality and morbidity and human rights" par. 6.