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The Relationship of Abortion and Violence Against Women: Violence Prevention Strategies and Research Needs

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Risk of HIV Infection in Depot-Medroxyprogesterone Acetate (DMPA) Users: A Systematic Review and Meta-Analysis

Joel Brind, Ph.D.; Steven J. Condly, Ph.D.; Steven W. Mosher, M.S., M.A.; Anne R. Morse, B.A.; and Jennifer Kimball, Be.L.

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Proceedings of the Matthew Bulfin Educational Conference Washington, D.C., February 21-22, 2015

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Preface

This edition features a report of the Division 48 Presidential Task Force of the American Psychological Association, which examines the relationship of abortion and violence against women. From the perspective of peace psychology, the role of abortion in acts of violence against women is explored, with a focus on violence-prevention strategies. Setting aside the political debate, this Task Force report takes the conflict-transformation approach of considering all perspectives that have concern for the right of women to avoid being victims of violence. The evidence that victims of Intimate Partner Violence are disproportionately represented in women presenting for abortion suggests a need for screening at clinics. Coerced abortion is a form of violence and has occurred by government policy in China and as a result of other violence against women, including sex trafficking and war. Sex-selection abortion of female fetuses, referred to as "gendercide," has reached pandemic proportions and caused a gender imbalance in some countries. Psychology, through empirical research, can make unique contributions to understanding the relationship between abortion and violence, and in developing prevention strategies.

The second article in this edition, by Joel Brind, Ph.D. et al., provides a systematic review and meta-analysis of the risk of HIV infection in Depot-Medrosyprogesterone Acetate (DMPA) users. The authors searched Medline using the search terms: contraceptives or contraception and HIV and searched the bibliographies of articles thus identified. They included in the meta-analysis all studies examining the association between the use of DMPA (or injectable contraceptives comprising mostly DMPA) and the presence (cross-sectional studies) or acquisition (longitudinal studies) of HIV+ status in women, using a random effects models to estimate odds ratios (ORs; cross-sectional studies) and hazard ratios (HRs; longitudinal studies). Studies were excluded if the comparison group included women using any form of steroidal contraception.

Statistically significant positive associations between DMPA use and HIV positivity were observed both in cross-sectional and longitudinal studies. The biological plausibility of increased vulnerability to HIV infection due to progestational action via thinning of the vaginal epithelial barrier and immunosuppression, as well as glucocorticoid agonistic immunosuppression, are discussed. The epidemiological and biological evidence make a compelling case that DMPA adds significantly to the risk of male-to-female HIV transmission.

The *Verbatim* section consists of the Proceedings of the Matthew Bulfin Educational Conference in Washington, D.C., February 21-22, 2015, sponsored by the American

Association of Pro-Life Obstetricians & Gynecologists. It includes short essays, summaries, and outlines of the presentations on (1) the biology of induced abortion and risk of breast cancer; (2) recent evidence showing a robust link between abortion and breast cancer; (3) the use of isomolecular progesterone in the support of pregnancy; (4) the reversal of mefepristone, (5) practicing medicine with integrity in a hostile culture; (6) the impact of physician compromise; (7) brain development in adolescents in regard to medical decisionmaking; (8) options for clinical intervention in sexual decisionmaking; (9) the myth that abortion is safer than childbirth; (10) Misoprostol and Oxytocin for postpartum hemorrhage; (11) the neuroanatomy and physiology of pain perception in the fetus; and (12) Levonorgesrel "emergency contraception."

This edition completes thirty years of publishing *Issues in Law & Medicine*. The editors wish to express their heartfelt appreciation for the co-sponsorship of the Watson Bowes Research Institute as we continue publishing scholarly articles for physicians, lawyers, and other professionals defending the medical treatment rights of persons who are medically dependent and persons with disabilities.

Barry A. Bostrom, J.D.
Editor-in-Chief

Articles

The Relationship of Abortion and Violence Against Women: Violence Prevention Strategies and Research Needs*

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ABSTRACT: From the perspective of peace psychology, the role of abortion in acts of violence against women is explored, with a focus on violence-prevention strategies. Setting aside the political debate, this task force report takes the conflict-transformation approach of considering all perspectives that have concern for the right of women to avoid being victims of violence. The evidence that victims of Intimate Partner Violence are disproportionately represented in women presenting for abortion suggests a need for screening at clinics. Coerced abortion is a form of violence and has occurred by government policy in China and as a result of other violence against women: sex trafficking and war situations. Sex-selection abortion of female fetuses, referred to as "gendercide," has reached pandemic proportions and caused a gender imbalance in some countries. Psychology, through empirical research, can make unique contributions to understanding the relationship between abortion and violence and in developing prevention strategies.
Keywords: Abortion, Violence against Women, Intimate Partner Violence, Coerced Abortion, Gendercide.

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Introduction

In recent decades, the United Nations and other human rights organizations have drawn attention to a specific form of violence, *gender-based violence*. The UN Declaration on the Elimination of Violence against Women defined violence against women as "any act of gender-based violence that results in, or is likely to result in, physical, sexual or psychological harm or suffering to women" (1993).

"Gender-based violence includes a host of harmful behaviors that are directed at women and girls because of their sex, including wife abuse, sexual assault, dowry-related murder, marital rape, selective malnourishment of female children, forced prostitution, female genital mutilation, and sexual abuse of female children" (Heise, Ellsberg, & Gottmoeller, 2002, p. S6). As discussed below, we suggest two important additions: coerced abortion (a woman's abortion decision is not made on her own volition and may include threats and pressure from others) and gendercide (sex selection abortion on a massive scale).

While abortion remains a highly controversial public policy issue, we are setting aside that controversy and instead focus on developing a research agenda concerning abortion from a peace psychology perspective. Peace psychology is a division of psychology which focuses on peace among nations and within communities and families, and prevention of destructive conflict and violence through conflict resolution. Psychological knowledge and methods are used to foster communication and research on conflictual topics toward a goal of violence prevention. Regarding abortion, the peace psychology perspective would attempt to find areas of agreement in which researchers from multiple perspectives might be able to collaborate. More specifically, we are interested in examining the relationship between violence and abortion for the purpose of preventing destructive conflict and injury, and empowering women's reproductive decision-making. The relevant scientific literature will be reviewed, gaps in knowledge identified, and suggestions for future research offered. Current research will be discussed in terms of its application toward preventing violence against women.

Intimate Partner Violence

Intimate Partner Violence (IPV) has been estimated to affect 20-25% of adolescent and adult women in the United States (Silverman, Raj, Mucci & Hathaway, 2001; Tjaden & Thoennes, 1998). While IPV may be perpetrated by both men and women and either sex may be victims, our focus is on violence against women. A form of domestic violence (which also includes child abuse and elder abuse), IPV may be inflicted as physical or sexual violence and is often accompanied by emotional abuse (Watts & Zimmerman, 2002). In a violent and/or abusive relationship, the victim may experience reproductive coercion and denied control of her own fertility. The notion of "reproductive coercion" has been defined by Miller and Silverman (2010) as "male partners' attempts to promote pregnancy in their female partners through verbal pressure and threats to become pregnant (pregnancy coercion), direct interference with contraception (birth-control

sabotage), and threats and coercion related to pregnancy continuation or termination (control of pregnancy outcomes)" (p. 2).

In the case of pregnant women, some clinicians have observed that batterers beat their pregnant partners' bellies and display regressions that seem to indicate rage at the fetus they believe competes for their partner's love. Such observations appear to be supported by women who were queried about their beliefs as to why their partners beat them during pregnancy (Campbell, Oliver, & Bullock, 1993). Incidence estimates of IPV during the perinatal period are reported to range from 3% to 17% (McMahon & Armstrong, 2012) and from 1.2% to 51% (Pool, Otupiri, Owusu-Dabo, de Jonge, & Agyemang, 2014). IPV that occurs during pregnancy may be best predicted by the severity and frequency of IPV that occurs over the course of a relationship (Campbell, Oliver, & Bullock, 1993).

Research findings indicate women with a history of IPV are significantly more likely to experience unintended pregnancy (Campbell & Soeken, 1999; Pallito et al., 2013) as well as rapid repeat pregnancy (Jacoby, Gorenflo, Black, Wunderlich, & Eyler, 1999; Scribano, Stevens & Kaizar, 2013). Since unplanned and unwanted pregnancy are common reasons for choosing abortion, it is not surprising that IPV has been found to be associated with elective abortion (Fanslow, Silva, Whitehead, & Robinson, 2008; Hall, Chappell, Parnell, Seed, & Bewley, 2014; Pallito et al. 2013; Saftlas et al., 2010; Taft & Watson, 2007). In one study (Leung, Leung, Chan, & Ho, 2002), 27.3% of women stated their experience of abuse influenced their decision to abort. Two other studies (Glander, Moore, Michielutte, & Parsons, 1998; Woo, Fine, & Goetzl, 2005) reported that women who experience IPV are less inclined to discuss abortion with abusive partners due to fear, and Silverman et al. (2010) observed that men who perpetrated IPV were more likely to report conflicts with their female partners concerning abortion. Men who are determined to control partners may insist on abortions their partners do not want (as in the famous case of Lorena Bobbit). Women who opt for abortion willingly or under threat may be experiencing multiple assaults from partners before and immediately after undergoing the procedure, putting their physical and emotional health at risk. Given the consistently observed association between IPV and abortion, there have been calls to screen women for a history of abuse during abortion counseling (Glander et al., 1998; Saftlas et al., 2010; Silverman et al., 2010; Wiebe & Janssen, 2001).

Repeat abortion is associated with a history of physical and sexual abuse (Fisher et al., 2005) and it is estimated that half of U.S. women obtaining abortion have had at least one previous abortion (Jones, Finer, & Singh, 2010). Steinberg and Russo (2008) reported that "multiple abortions were found to be associated with much higher rates of PTSD and social anxiety; this relationship was largely explained by pre-pregnancy mental health disorders and their association with higher rates of violence" (p. 238). Fisher et al. (2005) have suggested "Presentation for repeat abortion may be an important indication to screen for a current or past history of relationship violence and sexual abuse" (p. 637). It has been determined that "reducing IPV by 50% could potentially

reduce unintended pregnancy by 2%-18% and abortion by 4.5%-40%, according to Population Attributable risk estimates (Pallito et al., 2013, p. 3). Therefore, routine screening for current or past abuse of women seeking abortion may be an effective means of reducing violence against them (Glander et al., 1998; Saftlas et al., 2010; Silverman et al., 2010; Wiebe & Janssen, 2001).

Coerced Abortion

"Reproductive control," a concept similar to "reproductive coercion" is defined by Moore, Frohwirth, & Miller (2010) as occurring when partners, parents, peers, or the medical establishment "demand or enforce their own reproductive intentions whether in direct conflict with or without interest in the woman's intentions, through the use of intimidation, threats, and/or actual violence" (p. 2). Forcing a woman to become pregnant or complete a pregnancy against her wishes or forcing her to abort a pregnancy she desires to continue are forms of reproductive control. However, this paper is on the role of abortion in violence against women and therefore focuses on what is generally agreed about coerced abortion. Coerced child bearing is a separate subject deserving of its own attention and research agenda.

Forced abortion has been condemned as a "violation of our human rights" by the International Community of Women Living with HIV/AIDS (ICW, 2008). Research findings suggest that coercion and pressure to abort are not uncommon (Broen, Moum, Bodtker & Ekeberg, 2005; Hathaway, Willis, Zimmer & Silverman, 2005; Rue, Coleman, Rue & Reardon, 2004; Williams, 2000). However, studies report differing rates of coercion or pressure. Clearly then, more research is needed to establish accurate prevalence.

Coercion via Government Policy

In some countries, most prominently China, forced abortion is official governmental policy. Since 1978, Chinese couples are required to obtain "birth permits" to have children and are limited to only one child. Women without the required permit, or who are pregnant for the second or third time, "have been required, persuaded, and even forced by the authorities to abort fetuses no matter how much they want to give birth" (Nie, 1999, p. 463). Cases of women being forced to abort even late in pregnancy have been documented by Women's Rights without Frontiers ("Cases," n.d.) and reported in Congressional testimony (*The Consequences of Coercion,* 2009). Reggie Littlejohn stated "The one-child policy is an issue about which pro-life people and pro-choice people can agree. No one supports forced abortion, because it is not a choice" (*The Consequences of Coercion,* 2009, p. 1). Former Secretary of State Hillary Clinton condemned forced abortion at the Fourth World Conference on Women in Beijing (Clinton, 1995) and Felice Gaer, pro-choice director of the Jacob Blaustein Institute for the Advancement of Human Rights, labeled coerced abortion as fitting "into the definition of torture" (Starr, 2009).

Coercion in Sex Trafficking

According to Lederer and Wetzel (2014), "The prevalence of forced abortions is an especially disturbing trend in sex trafficking" (p. 73). Women and girls forced into

sex trafficking, and those who choose to work as prostitutes, may experience forced abortion (Abdulraheem & Oladipo, 2010; Acharya, 2008; Diep, 2006; Hoyle, Bosworth, & Dempsey, 2011; Zimmerman, Hossain & Watts, 2011). In 2011, the American Psychological Association (APA) established a task force on sex trafficking and its report acknowledged a need for research on the long-term effects of "forced abortions on survivors' sexual and reproductive health" (APA, 2013, p.21).

Women trafficked for sex are often subjected to multiple abortions, risking health problems (Cwikel, Chudakov, Paikin, Agmon, & Belmaker, 2004; U.S. Justice Department, n.d.). Some women are forced to abort during late pregnancy and to resume sex work only days later (Getu, 2006). According to a sex trafficking expert in Wichita, Kansas in the United States, pregnant women are in demand due to consumer fetishes. As a result, they carry their pregnancies nearly to term and are then forced to abort (personal communication, March 2014). Another expert in human trafficking confirmed this claim that forced abortion is directly related to pregnancy fetishes (personal communication, July 2014).

Trafficking of humans for sex has numerous serious public health implications (Huda, 2006; Lederer & Wetzel, 2014) including "sexually transmitted diseases, pelvic inflammatory disease, hepatitis and tuberculosis. Unwanted pregnancy, forced abortion, and abortion-related complications are other causes of health problems among trafficked persons" (Getu, 2006, p. 149; Zimmerman et al., 2011). Despite the increased risk for life-threatening health consequences, "Traffickers typically do not allow victims to seek health care—unless it is for an abortion, in which case, the cost of the abortion is added to any outstanding debt the woman owes" (Riegler, 2007, p. 243). Of those women who did report having seen a health care provider while being trafficked, only about one- half of them believed the doctor recognized they were sex workers and even then, doctors did not understand that the women were being trafficked (Lederer & Wetzel, 2014).

According to Stephen Wagner, former director of the Human Trafficking Program at the Department of Health and Human Services, "The mortality rate for someone in commercial sexual exploitation is 40 times higher than for a non-exploited person of the same age. Helping a victim return to exploitation more quickly by terminating a pregnancy increases the odds of death" (2011).

Coercion in War

During wartime, women are frequently subjected to sexual violence through rape, sexual slavery, forced pregnancy, forced sterilization, and forced abortion which may be used as a form of genocide (Amowitz & Reiss, 2004; Askin, 2003; Bennett, Bartlett, Olalunde & Amowitz, 2004). While several international treaties outlaw rape during war, they have not proven to be effective in protecting women (Aydelott, 1993). Women living in war zones may experience the compounded trauma of both coerced sex and coerced abortion.

Shame may be a powerful coercive force among women seeking abortion after being impregnated by wartime rape. Shortly after World War II, many Korean women who

were raped by Japanese soldiers died "either from untreated venereal disease, beatings, botched abortions, or the effects of deprivation" (Aydelott, 1993, p. 596). In the 1971 war between Bangladesh and West Pakistan, hundreds of thousands of Bengali women were raped by Pakistani soldiers (Neill, 2013). The racial differences "added to the shame and suffering of Bengali women who became pregnant after being raped, for it was made known in Bangladesh after the war that the Bengali women and the children they bore with Punjabi features would never be accepted back into Bengali culture" (p. 46). As a result, women felt extreme pressure to abort or resorted to infanticide or suicide.

In post war Germany, thousands of women in Berlin were raped by Soviet soldiers (Lichtblau, 2013; Anonymous, 2005). Grossmann (1995) notes that while nonmedical and noneugenic abortion was illegal in Germany, "the other side of harsh wartime regulations limiting abortion and access to contraceptives were secret directives permitting — or coercing — abortions on female foreign workers and women defined as prostitutes and non-"Aryans," as well as on the growing number of German women who became pregnant, via consensual sex or rape, by foreign workers or prisoners of war" (p. 52).

The development of PTSD among women who experience rape is well documented (Faravelli, Giugni, Salvatori, and Ricca, 2004, Kilpatrick, Edmunds, & Seymour, 1992; Rothbaum, Foa, Riggs, Murdock, and Walsh, 1992). When women become pregnant from rape and are forced or feel pressured to abort, they may be further traumatized. Future research is needed beyond individual case studies to determine the extent to which coerced abortion after rape may or may not contribute its own additional measure of trauma.

Another effect of war, limited access to basic resources, may create pressure on women to abort. The abortion rate rose steeply in Sarajevo while occupied by Serbian forces in 1993. Referring to her abortion, a Bosnian woman stated, "I would never do this in peacetime. And God knows I wanted this child, but there is no food for him in my house" (Meehan, 2012). After the 2003 invasion of Iraq resulted in a mass exodus of physicians, prenatal and obstetric care were severely limited. Many Iraqi women felt pressured to abort because they were "unable to get medical care for themselves and their unborn" (Meehan, 2012).

Environmental disasters are often caused by war. Even when they occur independently of war, they may pose another source of pressure for abortion. For example, following the Chernobyl nuclear accident in 1986, there were reports that induced abortion increased in the most contaminated areas (Pershagen, 1988). In Greece, it was estimated that 23% of pregnancies were aborted due to fears of fetal harm from radiation (Trichopoulus et al., 1987). Denmark also saw an increase in the rate of induced abortion in the months following the accident; "anxiety among the pregnant women and their husbands caused more fetal deaths in Denmark than the accident" (Knudsen, 1991, p. 229).

Forced abortion has also been reported to occur among women cadres of the Revolutionary Armed Forces of Columbia also known as the "FARC" (Stanski, 2005). Sexual

relations among male and female cadres are highly regulated. Females are required to use contraceptives, most frequently Norplant implants, injectable contraceptives, birth control pills, and condoms. Pregnancies are not allowed and abortions are forced upon women who do not voluntarily choose to abort. Some of the female members of the FARC, including minors, are also sexually exploited in a number of ways by their older male cadres.

Coercion or Pressure by Individuals

Male partners are frequently cited as the source of coercion (Broen et al., 2005; Hathaway, Willis, Zimmer & Silverman, 2005; Moore, Frohwirth & Miller, 2010) and may coerce women by threatening abandonment or even violence (Chamberlain & Levenson, 2012; Miller & Silverman, 2010). There have been a number of reports concerning women who were assaulted or murdered by the impregnating man because they would not submit to abortion (Blair, 2013; Clark, 2006; Dempsey, 2013; Jungen, 2013; Larrubia, 1998).

Coercion of minors by parents has also occurred. In a study of adolescent abortion, 18% of those minors whose parents found out about their pregnancies from a third party felt they were forced to abort and 6% of that same subset reported subjection to physical violence (Henshaw & Kost, 1992). Adolescent females may be especially vulnerable to coercion by parents, partners, or peers (Barglow & Weinstein, 1973) due to their dependency needs and developmental immaturity.

Coerced abortion has been used by adult men to hide incest or other sexual relationships with minor females (see, for example, Hutton, 2013). Some women, who sought abortion but then changed their minds, have been forced to abort by a provider who refused to stop the procedure (Bruce v. Hodari, 2009; Byer v. Doe, 2013; Gravely v. Stephens, 2013). The much publicized case against Dr. Kermit Gosnell included reports of such cases. The official grand jury report stated: "Gosnell began an abortion on a 29-week pregnant woman and then refused to take dilators out when the woman changed her mind" (Williams, 2011, p. 86). Two other patients who did not want to go through with the abortion were physically restrained, forcibly drugged, and subjected to abortion against their will (DiFilippo, 2011).

Some authors consider it important to distinguish between "coercion" and "pressure." However, the distinction is not often clear and these constructs may be conceptualized more accurately as a continuum. For example, in a study of male perpetrators of IPV, abusive men were significantly more likely to be involved in pregnancies ending in abortion than non-abusive men (Silverman et al., 2010). The extent to which this increase is due to actual coercion or to women feeling pressured was not determined. In some studies, the terms "pressure" and "coercion" are both used seemingly interchangeably, without either term being defined (Moore et al., 2010).

What is clear on both sides of the abortion debate is that both *coercion* (Allanson & Astbury, 1995; Franco, et al., 1989; Gibbons, 1984; Kero, Hogberg & Lalos, 2004; Moniq & Moron, 1982; Paul et al., 2009; Stotland, 2001, 2003; Turell, Armsworth &

Gaa, 1990; Zakus & Wilday, 1987) and *pressure* (Academy of Medical Royal Colleges, 2011; APA, 2008; Broen et al., 2005; Dagg, 1991; Kimport, Foster & Weitz, 2011; Major et al., 2009; Needle & Walker, 2008; Olson, 1980; Pope, Adler & Tschann, 2001; Stotland, 1997; Williams, 2001) are risk factors for women's psychological adjustment to abortion. Therefore, women who are screened for coercion and pressure are more likely to make autonomous decisions, receive needed support, and experience better outcomes. Screening is also likely to help identify women being exploited by traffickers and minors being sexually abused by adult males. Once identified, these women can be offered protection from further violence. In the National Abortion Federation's current textbook for abortion providers, "coercion" is included in a pre-abortion screening tool (Baker & Beresford, 2009).

Gendercide

Sex ratio imbalance was addressed at the Fourth World Conference on Women of the UN Commission on the Status of Women (1995) held in Beijing. Delegates included "prenatal sex selection and female infanticide" in their official definition of "violence against women." Former U.S. President Jimmy Carter (2014), in his recent book concerning women's rights, observed that 160 million fetuses have been aborted because they were female.

Little progress has been made in deterring the practice of gendercide through prenatal sex selection abortion. In an official report accepted by the European Parliament, Liisanantti & Beese (2012) noted the skewed sex ratios in many countries around the world including India, China, Vietnam, Albania, Azerbaijan, Georgia, Armenia, and among children of Asian parents in Great Britain, the United States, and Canada. Focusing on India and China, the authors identified three main factors: 1) falling fertility, 2) wide availability of ultrasound, allowing parents to learn the sex of their fetuses, and 3) a deeply entrenched preference for sons. In India, when ultrasound reveals a female fetus, "it is a societal norm that the family, particularly the mother-in-law and husband force the pregnant woman (to abort) and if she does not cooperate, she faces domestic violence and kicking on the abdomen. This is rampant in rich and poor, illiterate and educated" (interview with Vinita Shaw of the Disha Foundation, 2014).

Investigators are studying the problem of distorted sex ratios in various countries including China, where the ratio is "alarmingly skewed" in favor of males (Nie, 2011, p. 3), India, where males outnumber females by almost 40 million (Goldberg & Dooley, 2011), Vietnam (Becquet & Ceped, 2013), and several countries in Eastern Europe (Guilmoto & Duthe, 2013).

In her book, *Unnatural Selection,* Hvistendahl (2011) recounts how gender imbalances came about through advocates of population control and the development of technology to determine sex before birth. Hvistendahl identifies political individuals and organizations that actively supported using abortion for population control, including aborting primarily female fetuses. In commentary on Hvistendahl's book, Douthat (2011) states, "For many of these anti-population campaigners, sex selection was a

feature rather than a bug, since a society with fewer girls was guaranteed to reproduce itself at lower rates." Douthat also noted Hvistendahl's depiction of the "unlikely alliance between Republican cold warriors worried that population growth would fuel the spread of Communism and the left-wing scientists and activists who believed that abortion was necessary." Foster (1989) commented on population control as military strategy: "policymakers must … employ all the instruments of statecraft at their disposal (development assistance and population planning every bit as much as new weapon systems)" (p. 24). Abortion aimed at female fetuses may be considered by some as an acceptable and effective weapon.

An article in *The Economist* (2010) discussed societal consequences of gender imbalance. In China and India, rising crime rates are correlated with the increase in the ratio of males to females. Specifically, crimes against women such as rape, prostitution, and sex trafficking are becoming more prevalent. Both the United States Department of State (Lagon, 2008) and the Chinese Academy of Social Sciences have identified gender imbalance as a contributing factor to trafficking and forced prostitution (*China Faces Growing Gender Imbalance*, 2010). Thousands of Vietnamese women have been forcibly taken to China, compelled to work in brothels or sold as wives for Chinese men (Giang, 2002; Linh, n.d.). Women who are trafficked in India may be required to sleep with not just one man but "with his brothers as well" (Hvistendahl, 2011, p. 190). This was confirmed by Vinita Shaw who stated that in Haryana, India, it is a common practice for many brothers to share one woman as their wife (personal communication, July, 22, 2014).

Child marriage is increasing as women become increasingly scarce (Burns, 1998; Hvistendahl & Lindquist, 2008). Women sold to be brides often find themselves in abusive marriages. Among foreign wives living in Korea, 25% stated they felt physically threatened by their husbands (*Foreign Brides Rejuvenate Korea's Aging Society,* 2009). Forced marriage has become so common in Asia it is now recognized as a valid reason to petition for political asylum in the United States (Gao v. Gonzales, 2006). In countries where abortion is a form of discriminatory violence against unborn females, it appears to have precipitated even more violence against adult women and girls.

Suggestions for Future Research on Violence Prevention Strategies

Intimate Partner Violence

- Clarify the wide range of reported incidence of IPV during pregnancy which may be explained by differences in study designs, definitions and study populations (Shah & Shah, 2010).
- Identify the characteristics of male partners that may contribute to induced abortion among victims of IPV (Hall et al., 2014).
- Identify specific intermediate factors that may explain the association between IPV and abortion (e.g. fear, unintended pregnancy, pressure or coercion from male partners, pressure from others, stigma, shame, or other pressures related

to being an IPV victim). While multiple methodological approaches are available, qualitative research may be especially useful in identifying the influence of these intermediate factors.
- Develop and evaluate screening programs for victims of IPV in terms of success in identifying victims and protecting them from further violence including coerced abortion.
- Systematically evaluate the effectiveness of treatment programs for victims and/or perpetrators of IPV (Ellsberg & Heise, 2005; Hall et al., 2014; Stover, Meadows & Kaufman, 2009).
- Engage in large-scale, long-term studies to evaluate interventions aimed at reducing unintended pregnancy among women exposed to IPV (Miller et al., 2011).

Coercion

- Documentation of the extent and incidence of forced or coerced abortion globally.
- An exploration of the concept of "pressure" that identifies specific factors or conditions (e.g., economic, cultural, relational, intrapersonal, societal pressures from war or environmental disaster) that women perceive as causing them pressure to abort.
- Further examination of the long-term effects of coercion and pressure related to abortion on women's mental health.
- Development, implementation, and evaluation of screening tools to protect women from coerced and pressured abortion, and to provide evidenced-based support after abortion. Specifically, research needs to focus on how women should be screened, including (a) timing of screening, (b) method of screening, (c) questions aimed at uncovering coercion, and (d) the context in which screening occurs.
- Evaluations of legal interventions aimed at reducing sex trafficking and thereby reducing the number of sex-trafficked women who are coerced into abortion (e.g. Diep, 2006 notes that Sweden's criminalization of paying for sex services has dramatically reduced the number of women trafficked into Sweden).
- Evaluations of programs that train medical workers in general clinics and in abortion clinics to identify victims of sex trafficking.
- Explorations of the therapy needs of women who have been pressured or coerced into abortion and evaluations of therapy protocols developed for them.

Gendercide

- Identify psychological factors which influence the practice of gendercide.
- with quantitative and qualitative studies of attitudes among both citizens and medical professionals.

- Quantitative and qualitative studies of the immediate and long-term impact of gendercide via sex-selective abortion on women, men, couples, marital relationships, and siblings.
- Evaluations of interventions such as: compliance with international human rights laws (Tiefenbrun & Edwards, 2008), educational and public campaigns to raise awareness and improve the status of females (Manhas & Banoo, 2013), and financial incentives (Liisanantti & Beese, 2012) that may mitigate the practice of sex-selective abortions, thereby protecting unborn females and restoring normal sex-ratios.
- In-depth, qualitative studies to explore the experience of women who choose or are coerced to abort a fetus because of their shared gender. Such studies may be essential to recognize the effects on women's self-esteem, their sense of value as females, their mental health, and to identify women's therapeutic needs.
- Qualitative and quantitative studies to gather data concerning how sex-selective abortion affects women's attachment to and parenting of existing and future children and whether these vary depending on the children's sex.

Conclusion

There is a global awareness that violence against women is a serious and widespread issue and a growing consensus that this issue demands attention and intervention if women are to be protected. Intimate partner violence, reproductive coercion, and gendercide are all recognized forms of violence against women. Induced abortion is also a form of violence against women when it is forced upon women against their will or used to eliminate female fetuses.

Given that a considerable amount of the literature pertaining to IPV, reproductive coercion, and gendercide comes from disciplines other than psychology, the latter has a unique contribution to make on its own or in collaboration with other disciplines. Peace psychology in particular, with its emphasis on the causes of violence, may offer a most useful and appropriate context in which to study these topics and develop violence prevention strategies.

In an effort to be consistent with peace psychology's emphasis on conflict resolution, we have deliberately chosen to focus on areas where consensus is possible and prevention is vital. While heated debate may continue concerning the psychological aftermath of induced abortion, we believe that in the contexts of IPV, coerced abortion, and gendercide, there is a consensus upon which scientific studies and interventions can be developed that will protect women from violence and help those who have been victimized.

References

Abdulraheem, S. & Oladipo, A.R. (2010). Trafficking in women and children: A hidden health and social problem in Nigeria. *International Journal of Sociology and Anthropology,* 2 (3), 034-039.

Academy of Medical Royal Colleges (2011). *Induced abortion and mental health –A systematic review of the mental health outcomes of induced abortion, including their prevalence and associated factors.* London: Academy of Medical Royal Colleges/National Collaborating Center for Mental Health.

Acharya, A. K. (2008). Sexual violence and proximate risks: A study on trafficked women in Mexico City. *Gender, Technology and Development*, *12*(1), 77-99.

Allanson, S. & Astbury, J. (1995). The abortion decision: Reasons and ambivalence. *Journal of Psychosomatic Obstetrics and Gynaecology, 16* (3), 123-136.

American Psychological Association, Task Force on Mental Health and Abortion. (2008). *Report of the task force on mental health and abortion.* Washington, DC. Retrieved from http://www.apa.org/pi/wpo/mental-health-abortion-report.pdf.

American Psychological Association, (2013). *Report of the task force on trafficking of women and girls.* Washington, DC. Retrieved from http://www.apa.org/pi/women/programs/trafficking/executive-summary.pdf.

Amowitz, L. & Reis, C. (2004, November). *War-related sexual violence in Sierra Leone*. In the 132nd Annual Meeting.

Anonymous, (2005). *A woman in Berlin: Eight weeks in the conquered city.* New York, NY: Metropolitan Books.

Askin, K.D. (2003). Prosecuting wartime rape and other gender-related crimes under international law: Extraordinary advances, enduring obstacles. *Berkeley Journal of International Law, 21* (2), 288-349.

Aydelott, D. (1993). Mass rape during war: Bosnian rapists under international law. *Emory International Law Review, 7,* 585-631.

Baker, A. & Beresford, T. (2009). Informed consent, patient education and counseling. *In* Paul, M., Lichtenberg, T.S., Borgatta, L., Grimes, D.A. Stubblefield, P.G. & Creinin, M.D. (Eds.) *Management of unintended and abnormal pregnancy.* Chichester, U.K.: Wiley-Blackwell.

Barglow, P. & Weinstein, S. (1973). Therapeutic abortion during adolescence: Psychiatric observations. *Journal of Youth and Adolescence, 2*(4), 331-342.

Becquet, V. & Ceped, P. (2013). *From gender inequality to prenatal sex selection: Comparative analysis of son preference in Hai Duong and Ninh Thuan provinces, Vietnam*. Retrieved from the International Union for the Scientific Study of Population website at: http://www.iussp.org/sites/default/files/event_call_for_papers/From%20gender%20inequality%20to%20prenatal%20sex%20selection%20Vietnam%20_BECQUET%20LE_0.pdf.

"Beijing Declaration and Platform for Action," Fourth World Conference on Women, Beijing, China, September 4-15, 1995, www.uneca.org/acgd/gender/en_beijing.doc.

Bennett, T., Bartlett, L., Olalunde, O.A. & Amowitz, L. (2004). Refugees, forced displacement and war. *Emerging Infectious Diseases, 10* (11), 2034-2035.

Blair, L. (2013). Man charged with murder after allegedly tricking girlfriend into taking abortion pill. *The Christian Post.* Retrieved from http://www.christianpost.com/news/man-charged-with-murder-after-allegedly-tricking-girlfriend-into-taking-abortion-pill-96123/.

Broen, A.N., Moum, T., Bodtker, A.S. & Ekeberg, O. (2005). Reasons for induced abortion and their relation to women's emotional distress: A prospective, two-year follow-up study. *General Hospital Psychiatry, 27* (1), 36-43.

Bruce, C. v. Hodari, A.A. (2009). Retrieved from http://operationrescue.org/pdfs/brucevshodari.pdf.

Burns, J.F. (1998). Though illegal, child marriage is popular in part of India. *New York Times*, May 11, Retrieved from http://tinyurl.com/4mtcqrg.

Byer, A. v. Doe, J. (2013). Retrieved from http://www.adfmedia.org/files/ByerComplaint.pdf.

Campbell, J. C., Oliver, C., & Bullock, L. (1993). Why battering during pregnancy? *AWHONN's Clinical Issues in Perinatal and Women's Health Nursing, 4*(3), 343-349.

Campbell, J.C. & Soeken, K.L. (1999). Forced sex and intimate partner violence: Effects on women's risk and women's health. *Violence against Women, 5*(9), 1017-1035.

Carter, J.E. (2014). *A call to action: Women, religion, violence, and power.* New York: Simon & Schuster.

Cases (n.d.). Retrieved from: http://www.womensrightswithoutfrontiers.org/index.php?nav=cases.

Chamberlain, L. & Levenson, R. (2012). *Addressing intimate partner violence, reproductive coercion and sexual coercion: A guide for obstetric, gynecologic and reproductive health care settings.* The American College of Obstetricians and Gynecologists.

China faces growing gender imbalance. (2010). BBC, January 11. Retrieved from http://news.bbc.co.uk/2/hi/8451289.stm.

Clark, v. (2006). Mothers-to-be's killer gets life terms. *The Inquirer*. Retrieved from http://articles.philly.com/2006-10-18/news/25418065_1_life-terms-search-la-toyia-Figueroa.

Clinton, H. (1995). "Remarks for the United Nations fourth world conference on women." Retrieved from http://www.un.org/esa/gopher-data/conf/fwcw/conf/gov/950905175653.txt.

The Consequences of Coercion: China's One Child Policy and Violence against Women and Girls. Hearing before the Tom Lantos Congressional Human Rights Caucus. November 10, 2009.

Cwikel, J., Chudakov, B., Paikin, M., Agmon, K. & Belmaker, R.H. (2004). Trafficked female sex workers awaiting deportation: Comparison with brothel workers. *Archives of Women's Mental Health, 7*, 243–9.

Dagg, P.K. (1991). The psychological sequelae of therapeutic abortion – denied and completed. *American Journal of Psychiatry, 148* (5), 578-585.

Dempsey, C. (2013). Warrant: Man had girlfriend killed because she was pregnant. *The Courant.* Retrieved from http://articles.courant.com/2013-06-07/community/hc-hartford-bryan-murder-arraignment-0608-2-20130607_1_girlfriend-killed-magnolia-street-police.

Diep, H. (2006). We pay—The economic manipulation of international and domestic laws to sustain sex trafficking. *Loyola University Chicago International Law Review, 2* (2), 309-331.

DiFilippo, D. (2011). Victims say abortion doctor scarred them for life. *Philly.com.* Retrieved from http://articles.philly.com/2011-01-21/news/27041098_1_abortion-doctor-abortion-clinic-one-treatment-room.

Douthat, R. (2011). 160 million and counting. *The New York Times: The Opinion Pages.* Retrieved from http://www.nytimes.com/2011/06/27/opinion/27douthat.html?_r=0.

Ellsberg, M.C. & Heise, L. (2005). *Researching violence against women: A practical guide for researchers and activists.* Washington DC, United States. World Health Organization, PATH.

Fanslow, J., Silva, M., Whitehead, A., Robinson, E. (2008). Pregnancy outcomes and intimate partner violence in New Zealand. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 48* (4), 391-7.

Faravelli, C., Giugni, A., Salvatori, S., & Ricca, V. (2004). Psychopathology after rape. *American Journal of Psychiatry*, *161*(8), 1483-1485.

Fisher, W.A., Singh, S.S., Shuper, P.A., Carey, M., Otchet, F., MacLean-Brine, D., Bello, D.D. & Gunter, J. (2005). Characteristics of women undergoing repeat induced abortion. *CMAJ, 172* (5), 637-641.

Foreign brides rejuvenate Korea's aging society, (2009). Deutsche Presse-Agentur, October 28.

Foster, G. D. (1989). Global demographic trends to the year 2010: Implications for U.S. security. *Washington Quarterly, 12* (2), 5-24.

Franco, K., Tamburrino, M., Campbell, N., Pentz, J. & Jurs, S. (1989). Psychological profile of dysphoric women post abortion. *Journal of the American Medical Women's Association, 44* (4), 113-115.

Gao v. Gonzales, 04-1874-ag, 2nd Circuit Court of Appeals, (2006).

Gendercide: The world wide war on baby girls. (May 4, 2010). *The Economist.* Retrieved from www.economist.com/node/15636231.

Getu, M. (2006). Human trafficking and development: The role of microfinance. *Transformation, 23* (3), 142-156.

Giang, T.T. (2002). Vietnamese women fall prey to traffickers. *Asia Times,* September 27. Retrieved from http://tinyurl.com/47k3jbx.

Gibbons, M. (1984). Psychiatric sequelae of induced abortion. *Journal of the Royal College of General Practitioners, 34* (260), 146-150.

Glander, S.S., Moore, M. L., Michielutte, R. & Parsons, L.H. (1998). The prevalence of domestic violence among women seeking abortion. *Obstetrics and Gynecology, 91* (6), 1002-1006.

Goldberg, A.B. & Dooley, S. (2011). Disappearing daughters: Women pregnant with girls pressured into abortion. ABC News 20/20, De. 9, 2011. Retrieved from http://abcnews.go.com/Health/women-pregnant-girls-pressured-abortions-india/story?id=15103950#.UaWMkr4o5Zd.

Gravely, I. v. Stephens, R. L. (2013). Retrieved from http://www.adfmedia.org/files/GravelyComplaint.pdf.

Grossmann, A. (1995). A question of silence: The rape of German women by occupation soldiers. *October,* 43-63.

Guilmoto, C.Z. & Duthe, G. (2013). *Masculinization of birth in Eastern Europe.* (No. 506). Institut National d'Etudes Demographiques (INED).

Hall, M., Chappell, L.C., Parnell, B.L., Seed, P.T. & Bewley, S. (2014). Associations between intimate partner violence and termination of pregnancy: A systematic review and meta-analysis. *PLOS Medicine, 11* (1), doi:10.1371.

Hathaway, J., Willis, G., Zimmer, B., & Silverman J. (2005). Impact of partner abuse on women's reproductive lives. *Journal of the American Medical Women's Association 60* (1), 42-45.

Heise, L., Elsberg, M. & Gottmoeller, M. (2002). A global overview of gender-based violence. *International Journal of Gynecology and Obstetrics, 78,* Suppl. 1, S5-S14.

Henshaw, S. & Kost, K. (1992). Parental involvement in minors' abortion decisions. *Family Planning Perspectives, 25* (4), 196-204.

Hoyle, C., Bosworth, M. & Dempsey, M. (2011). Labelling the victims of sex trafficking: Exploring the borderland between rhetoric and reality. *Social and Legal Studies, 20* (3), 313-329. doi: 10.1177/0964663911405394.

Huda, S. (2006). Sex trafficking in south Asia. *International Journal of Gynecology and Obstetrics, 94,* 374-381.

Hutton, C. (2013, May 16). Everson rapist gets prison for impregnating girl, making her get abortion. *The Bellingham Herald.*

Hvistendahl, M. (2011) *Unnatural selection: Choosing boys over girls, and the consequences of a world full of men.* New York: PublicAffairs, 2011.

Hvistendahl, M. & Lindquist, A. (2008). Half the sky: How China's gender imbalance threatens its future. *Virginia Quarterly Review, 84* (4). Retrieved from http://www.vqronline.org/dispatch/half-sky-how-china%E2%80%99s-gender-imbalance-threatens-its-future.

International Community of Women Living with HIV/AIDS (ICW). (2008). *Addressing the needs of HIV-positive women for safe abortion care.* London, ICW.

Jacoby, M., Gorenflo, D., Black, E., Wunderlich, C., & Eyler, AE. (1999). Rapid repeat pregnancy and experiences of interpersonal violence among low-income adolescents. *American Journal of Preventive Medicine, 16* (4):318–321.

Jones, R.K., Finer, L.B. & Singh, S. (2010). *Characteristics of U.S. abortion patient, 2008s.* New York: Guttmacher Institute.

Jungen, A. (2013). Man charged with threatening woman who refused abortion. *The LaCrosse Tribune.* Retrieved from http://lacrossetribune.com/news/local/man-charged-with-threatening-woman-who-refused-abortion/article_69045fr32-8551-11e2-9aad-0019bb2963f4.html.

Kero, A., Hogberg, U. & Lalos, A. (2004). Well-being and mental growth—long-term effects of legal abortion. *Social Science and Medicine, 58* (12), 2559-2569.

Kilpatrick, DG.; Edmunds, CN.; Seymour, AK. (1992). *Rape in America: A report to the nation.* National Victim Center; Arlington, VA.

Kimport, K., Foster, K, & Weitz, T. (2011). Social sources of women's emotional difficulty after abortion: Lessons from women's abortion narratives. *Perspectives on Sexual and Reproductive Health, 43*(2), 103-109.

Knudsen, L.B. (1991). Legally induced abortions in Denmark after Chernobyl. *Biomedicine & Pharmacotherapy, 45* (6), 229-231.

Lagon, M. (2008). *Missing girls in Asia: Magnitudes, implications, and possible responses.* (panel discussion), American Enterprise Institute, Washington, D.C., September 17.

Larrubia, E. (1998). Jury convicts man in ex-girlfriend's slaying. *The Los Angeles Times*. Retrieved from http://articles.latimes.com/1998/may/21/local/me-52107.

Lederer, L. & Wetzel, C. (2014). The health consequences of sex trafficking and their implications for identifying victims in health care facilities. *Annals of Health Law, 23* (1), 61-91.

Leung, T.W., Leung, W.C., Chan, P.L. & Ho P.C. (2002). A comparison of the prevalence of domestic violence between patients seeking termination of pregnancy and other general gynecology patients. *International Journal of Gynecology and Obstetrics 77* (1), 7-54.

Lichtblau, E. (2013). The holocaust just got more shocking. *New York Times,* (March 1).

Liisanantti, A. & Beese, K. (2012). *Gendercide: The missing women?* European Parliament, Directorate-General for External Policies. Retrieved from http://www.europarl.europa.eu/RegData/etudes/etudes/join/2012/433777/EXPO-DEVE_ET(2012)433777_EN.pdf.

Linh, H.T.T. (n.d.). *Cross border trafficking in Quang Ninh Province,* International Organization for Migration (paper distributed by Hanoi office). Retrieved from http://tinyurl.com/4okg7yx.

Major, B., Applebaum, M., Beckman, L. Dutton, M., Russo, N. & West, C. (2009). Abortion and mental health: Evaluating the evidence. *American Psychologist, 64* (9), 863-890.

Manhas, S. & Banoo, J. (2013). A study of beliefs and perceptions related to female foeticide among Muslim community in Jammu, Jammu and Kashmir, India. *Studies on Home and Community Science, 7* (2), 125-130.

McMahon, S. & Armstrong, D.Y. (2012). Intimate partner violence during pregnancy: Best practices for social workers. *Health & Social Work.* doi: 10.1093/hsw/hls004.

Meehan, M. (2012, January 16). In harm's way: Children, born and unborn, trapped in wartime. *America: The National Catholic Weekly*; Retrieved from http://americamagazine.org/node/150381.

Miller, E., Decker, M.R., McCauley, H.L., Tancredi, D.J., Levenson, R.R., Waldman, J., Schoenwald,P. & Silverman, J.G. (2011). A family planning clinic partner violence intervention to reduce risk associated with reproductive coercion. *Contraception, 83* (3), 274-280.

Miller, E. & Silverman, J. (2010). Reproductive coercion and partner violence: Implications for clinical assessment of unintended pregnancy. *Expert Review of Obstetrics and Gynecology, 5*(5), 511-515.

Moniq, C. & Moron, P. (1982). Psychological aspects of induced abortion. *Psychologie Medicale, 14*(8), 1181-1185.

Moore, A.M., Frohwirth, L. & Miller E. (2010). Male reproductive control of women who have experienced intimate partner violence in the United States. *Social Science and Medicine, 70* (11), 1737-44. doi: 10.1016/j.socscimed.2010.02.009. Epub 2010 Mar 9.

Needle, R. & Walker, L. (2008). *Abortion counseling: A clinician's guide to psychology, legislation, politics, and competency.* New York: Springer Publishing Company.

Neill, K. G. (2013). Duty, honor, rape: Sexual assault against women during war. *Journal of International Women's Studies*, *2*(1), 43-51.

Nie, J. B. (1999). The Problem of Coerced Abortion in China and Related Ethical Issues. *Cambridge Quarterly of Healthcare Ethics*, 8(04), 463-75.

Olson, J. (1980). Social and psychological correlates of pregnancy resolution among adolescent women: A review. *American Journal of Orthopsychiatry, 50,* 432-445.

Pallito, C.C., Garcia-Moreno, C., Jansen, H., Heise, L., Ellsberg, M. & Watts. C. (2013). Intimate partner violence, abortion, and unintended pregnancy: Results from the WHO multi-country study on women's health and domestic violence. *International Journal of Gynecology and Obstetrics, 120,* 3-9.

Paul, M. Lichtenberg, E., Borgatta, L., Grimes, D., Stubblefield, P. & Creinen, M. (2009). *Management of unintended and abnormal pregnancy: Comprehensive abortion care*. West Sussex, UK: Blackwell Publishing.

Pershagen, G. (1988). Health effects of Chernobyl. *British Medical Journal, 297* (6662), 1488-1489.

Pool, M.S., Otupiri, E., Owusu-Dabo, E., de Jonge, A. & Agyemang, C. (2014). Physical violence during pregnancy and pregnancy outcomes in Ghana. *BMC Pregnancy and Childbirth, 14* (71). doi:10.1186/1471-2393-14-71.

Pope, L.M., Adler, N.E. & Tschann, J.M. (2001). Postabortion psychological adjustment: Are minors at increased risk? *Journal of Adolescent Health, 29* (1), 2-11.

Riegler, A. (2007). Missing the mark: Why the trafficking victims protection act fails to protect sex trafficking victims in the United States. *Harvard Journal of Law &Gender*, *30*, 231.

Rothbaum, B.O., Foa, E.B., Riggs, D., Murdock, T. & Walsh, W. (1992). A prospective examination of post-traumatic stress disorder in rape victims. *Journal of Traumatic Stress, 5*, 455-475.

Rue, V.M., Coleman, P.K., Rue, J.J. & Reardon, D.C. (2004). Induced abortion and traumatic stress: A preliminary comparison of American and Russian women. *Medical Science Monitor, 10* (10): SR5-16. PMID: 15448616.

Saftlas, A. F., Wallis, A. B., Shochet, T., Harland, K. K., Dickey, P., & Peek-Asa, C. (2010). Prevalence of intimate partner violence among an abortion clinic population. *American Journal of Public Health*, *100*(8).

Scribano, P.V., Stevens, J., Kaizar, E. & NFP-IPV Research Team (2013). The effects of intimate partner violence before, during, and after pregnancy in nurse visited first time mothers. *Maternal and Child Health Journal*, 17(2), 307-18.

Shah, P.S. & Shah, J. (2010). Maternal exposure to domestic violence and pregnancy and birth outcomes: A systematic review and meta-analyses. *Journal of Women's Health, 19* (11), 2017-2031.

Silverman, J.G., Decker, M.R., McCauley, H.L., Gupta, J., Miller, E., Raj, A. & Goldberg, A.B. (2010). Male perpetration of intimate partner violence and involvement in abortions and abortion-related conflict. *Research and Practice, 100* (8), 1415-1417.

Silverman, J.G., Raj, A., Mucci, L.A. & Hathaway, J.E. (2001). Dating violence against adolescent girls and associated substance use, unhealthy weight control, sexual risk behavior, pregnancy, and suicidality. *JAMA, 286* (5):572–579.

Stanski, K. (2005). Terrorism, gender, and ideology: A case study of women who join the Revolutionary Armed Forces of Columbia (FARC) *in* J.J. F. Forest (Ed.) *The Making of a Terrorist, Vol. I: Recruitment* (pp. 136-150). Westport, CT: Praeger Security International.

Steinberg, J. & Russo, N. (2008). Abortion and anxiety: What's the relationship? *Social Science & Medicine, 67,* 238-252.

Starr, P. (2009). *Prochoice human rights activists call Chinese abortion practices torture.* Retrieved from http://www.cnsnews.com/news/article/pro-choice-human-rights-activists-call-chinese-abortion-practices-torture.

Stotland, N.L. (1997) Psychosocial aspects of induced abortion. *Clinical Obstetrics and Gynecology, 40* (3), 673-686.

Stotland, N.L. (2001). Psychosocial aspects of induced abortion. *Archives of Women's Mental Health, 4,* 27-31.

Stotland, N.L. (2003). Abortion and psychiatric practice. *Journal of Psychiatric Practice, 9* (2), 139-149.

Stover, C. S., Meadows, A.L & Kaufman, J. (2009). Interventions for intimate partner violence: Review and implications for evidence-based practice. *Professional Psychology: Research and Practice, 40* (3), 223-233.

Taft, A.J. & Watson, L.F. (2007). Termination of pregnancy: associations with partner violence and other factors in a national cohort of young Australian women. *Australian and New Zealand Journal of Public Health, 31* (2), 135-142.

Tiefenbrun, S. & Edwards, C.J. (2008). Gendercide and the cultural context of sex trafficking in China. *Fordham International Law Journal, 32* (3), 730-780.

Tjaden, P. & Thoennes N. (1998). *Prevalence, Incidence and Consequences of Violence Against Women: Findings from the National Violence Against Women Survey.* Washington, D.C.: Department of Justice, National Institute of Justice.

Trichopoulos, D., Zavitsanos, X., Koutis, C., Drogari, P., Proukakis, C. & Petridou, E. (1987). The victims of Chernobyl in Greece: Induced abortions after the accident. *British Medical Journal (Clinical Research Edition), 295* (6606), 1100.

Turell, S.C., Armsworth, M.W. & Gaa, J.P. (1990). Emotional response to abortion: A critical review of the literature. *Women and Therapy, 9* (4), 49-68.

United Nations. *Declaration on the elimination of violence against women*. New York: United Nations General Assembly, 1993.

U.S. Justice Department. Resources: *Common health issues seen in victims of human trafficking.* Retrieved from http://www.justice.gov/usao/ian/htrt/health_problems.pdf.

Wagner, S. (2011). Kathleen Sebelius' gruesome moral calculus: Health and human services policy may be furthering the exploitation of sex-trafficked women. *National Catholic Register.* Retrieved from http://www.ncregister.com/daily-news/kathleen-sebelius-gruesome-moral-calculus.

Watts, C. & Zimmerman, C. (2002). Violence against women: Global scope and magnitude. *The Lancet, 359,* 1232-1237.

Wiebe, E.R. & Janssen, P. (2001). Universal screening for domestic violence in abortion. *Women's Health Issues, 11* (5), 436-441.

Williams, G. (2000). Grief after elective abortion: Exploring nursing interventions for another kind of perinatal loss. *Association of Women's Health, Obstetric and Neonatal Nurses Lifeline, 4* (2), 37-40.

Williams, G. (2001). Short-term grief after an elective abortion. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 30* (2), 174-183.

Williams, R.S. (January 14, 2011). *Report of the Grand Jury, Court of Common Pleas, First Judicial District of Pennsylvania* (PDF), Court of Common Pleas of Pennsylvania. Retrieved from http://www.phila.gov/districtattorney/pdfs/grandjurywomensmedical.pdf.

Woo J., Fine, P., & Goetzl, L. (2005). Abortion disclosure and the association with domestic violence. *Obstetrics and Gynecology 105* (6), 1329-34.

Zakus, G. & Wilday, S. (1987). Adolescent abortion option. *Social Work in Health Care, 12* (4), 77-91.

Zimmerman, C., Hossain, M. & Watts, C. (2011). Human trafficking and health: A conceptual model to inform policy, intervention and research. *Social Science & Medicine, 73* (2), 327-335.

Risk of HIV Infection in Depot-Medroxyprogesterone Acetate (DMPA) Users: A Systematic Review and Meta-analysis

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ABSTRACT:

Objective: As the HIV/AIDS epidemic continues to spread in Africa and Asia, use of the injectable contraceptive steroid DMPA is widespread and has been increasing. Since studies dating back to 1992 have suggested that DMPA may increase the transmission of HIV to women, we endeavored to determine if the extant epidemiological and biological evidence is sufficient to conclude that DMPA use constitutes a definite hazard to women's health.

Methods: We searched Medline using the search terms: contraceptives or contraception AND HIV and searched bibliographies of articles thus identified. We included in the meta-analysis all studies examining the association between use of DMPA (or injectable contraceptives comprising mostly DMPA) and the presence (cross-sectional studies, n = 8) or acquisition (longitudinal studies, n = 16) of HIV+ status in women, using a random effects

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models to estimate odds ratios (ORs; cross-sectional studies) and hazard ratios (HRs; longitudinal studies). Studies were excluded if the comparison group included women using any form of steroidal contraception.

***Results*: Statistically significant positive associations between DMPA use and HIV positivity were observed both in cross-sectional (OR = 1.41, 95% CI 1.15 - 1.73) and longitudinal studies (HR = 1.49, 95% CI 1.28 - 1.73). The biological plausibility of increased vulnerability to HIV infection due to progestational action (via thinning of the vaginal epithelial barrier and immunosuppression) as well as glucocorticoid agonistic immunosuppression, are discussed.**

***Conclusion*: The epidemiological and biological evidence now make a compelling case that DMPA adds significantly to the risk of male-to-female HIV transmission.**

Introduction

The HIV-AIDS epidemic continues to spread in the developing world, particularly in sub-Saharan Africa. While advocacy of condom use has been persistent and pervasive, family planning advocates have also pursued advocacy of steroidal contraceptives, even though these provide no protection against HIV transmission. In fact, evidence has accrued that links the use of steroidal contraception (SC, often referred to as "hormonal" contraception. We prefer the term "steroidal," since the compounds in question are, strictly speaking, steroid drugs and not actual hormones.) to increased risk of HIV transmission. In a 1999 meta-analysis,[1] Wang et al. observed a modest but significant association between HIV-1 seroconversion and oral contraceptive (OC) use. Since that time, injectable contraceptives (ICs)—especially DMPA—have been increasing in use compared to OCs. A number of studies have examined HIV-1 seroconversion as a function of IC use, and have found DMPA to facilitate HIV-transmission to an even greater extent than OCs. However, even though such evidence first appeared in the peer-reviewed literature over 20 years ago[2] and though this association has been examined in nearly two dozen studies since, no consensus has yet emerged as to the potential danger of HIV acquisition to women using DMPA. Even the authors of a systematic review as recent as 2013[3] declined to perform a meta-analysis of extant data, because the literature consisted of studies with "heterogeneous methods and mixed results." Most recently, two meta-analyses have appeared.[4,5] Importantly, these two reviews incorporated different criteria for inclusion and therefore summarized largely overlapping but somewhat different bodies of research, yet they reported almost identical, significant increased risks of HIV acquisition with DMPA use.

In the present article, we set out to assemble the literature pertaining to IC (particularly DMPA) and HIV acquisition and to quantify the overall findings of the worldwide literature. Considering the wide variation in population and primary study

methodology, we have endeavored to be as inclusive as possible in the meta-analysis, specifically aiming to avoid the imposition our own biases regarding quality criteria. Consequently, the present work contrasts sharply with both of the recently published meta-analyses by including many earlier studies, including many that had incorporated a less definitive, cross-sectional methodology.

We believe that the present work therefore provides a larger perspective on the role of contraceptive interventions in the unfolding of the global HIV-AIDS epidemic. Thus it may serve not only as potential confirmation of the work of others, but also as evidence of ways by which potential dangers that may be posed by the use of new interventions may be brought to light sooner. Such earlier warnings can impart life-saving information to both family planning practitioners and the women whose right it is make their own informed reproductive choices.

Methods

Eligibility Criteria and Study Selection

We searched the Medline data base using the terms "contraceptive" or "contraception" and HIV, to identify studies that examined HIV status or acquisition as a function of IC or DMPA use. We also searched bibliographies of studies so identified. All studies that reported risk estimates or crude data that could be converted into risk estimates were included, unless the comparison group also included women who were using some other form of steroidal contraception (e.g., a comparison between IC users and OC users). In our search, we did not impose any starting date criteria, so that the earliest relevant studies could be identified.

Since the overwhelming majority of women using IC use DMPA, we have endeavored, as much as possible, to focus on DMPA, especially in light of differences in affinity among synthetic progestins for progesterone and other steroid hormone receptors. Therefore, we have included all data specifically related to DMPA use, as well as data for which the progesterone agonist is not specified (as these refer mostly to DMPA), but have excluded data specifically pertaining to any other forms of IC (generally norethisterone) as well as data pertaining mostly or entirely to OCs.

A total of 34 studies were initially identified which contained data on the association of IC with HIV-1 seroconversion. Six studies[6-11] were excluded from the meta-analysis because the comparison group included women using other forms of SC, generally combined OCs. One study[12] was excluded because users of DMPA were lumped together with all "other" forms of contraception, and not separately analyzed. Of the remaining 25 reports, 4 were excluded[13-16] because their results were reported in subsequent papers as further follow-up on the same subjects. The meta-analysis therefore includes data from 24 studies reported in 23 papers[2, 17-38] (Ungchusak 1996[18] included both a cross-sectional and a longitudinal study). The eight cross-sectional and 16 longitudinal studies were analyzed separately.

Data Extraction and Analysis

All studies were reviewed to determine if they could provide OR (cross-sectional) or HR (longitudinal) effect size data. For studies which did not report ORs or HRs (e.g., those which reported ORs based on inappropriate comparisons[20] or those which reported incidence rate ratios or IRRs[18, 24, 26, 27]), we reconstructed, where possible, the raw data from which ORs or HRs could be calculated.

Some included studies used "crude" (unadjusted) data, whereas others reported data adjusted for a number of variables such as age, occupation, or marital status. We used multivariate-adjusted outcome statistics, where reported. Otherwise, we used either the reported unadjusted outcome statistics, or the basic 2x2 cell-type raw data.

Subjects of included studies differed substantially from study to study, e.g., in location (Asia versus Africa), employment (sex worker or not), age, condom use, etc. We therefore used the random effects model, which assumes that the various studies which are meta-analyzed represent a random sample of studies which represent the true effect.[39,40] We employed the statistical package "Comprehensive Meta-Analysis" (Version 2) by Biostat (Englewood Cliffs, NJ, USA).

Table I. Population Characteristics of Included Cross-sectional Studies.

Authors	Year of publication	Year(s) of study	Population size	Nation and locale	Subject source	Type of data presented
Siraprapasiri et al.[17]	1991	1989	238	Changmai, Thailand	CSW*	Crude OR
Rehle et al.[2]	1992	1990	356	Khon Kaen, Thailand	CSW	MLR**
Plourde et al.[20]	1992	1988-89	600	Nairobi, Kenya	STD clinic	Raw data
Kapiga et al.[21]	1994	1991-92	2,285	Dar-es-Salaam, Tanzania	family planning clinics	MLR
Ungchusak et al. [18]	1996	1990	271	Khon Kaen, Thailand	CSW	MLR
Taneepanichskul et al.[19]	1997	1993-94	376	northern Thailand	CSW	Crude OR
Kumwenda et al.[29]	2008	2003-05	1,686	Blantyre, Malawi	reproductive health clinics	CLR***
Leclerc et al.[30]	2008	2003-2006	4,549	Kenya, Lesotho, Malawi, Zimbabwe	General population	MLR

* Commercial sex workers, i.e. prostitutes

**Multiple Logistic Regression

***Conditional Logistic Regression

Table II. Population Characteristics of Included Longitudinal Studies

Authors	Yr of publication	Yr(s) of study	Pop. size	Nation and locale	Subject source	Months of follow-up	Follow up interval (months)	Type of data presented
Bulterys et al. [22]*	1994	1991-93	5,690	Butare, Rwanda	Prenatal clinics	24	24	Cum IR, MLR
Ungchusak et al.[18]	1996	1990-91	240	Khon Kaen, Thailand	CSW	3-12	3	IRR, MLR
Kiddugavu et al.[24]	2003	1994-99	5,117	Rakai, Uganda	General population	31	10	IRR, MLR
Baeten et al.[13, 14, 23]	2007	1993-97	779	Mombasa, Kenya	CSW	120	1	MV HR
Kleinschmidt et al.[26]	2007	1999-2001	551	Orange Farm, So. Africa	Family planning clinic	12	3	MV HR
Myer et al.[27]	2007	2000-04	4,073	Cape Town, So. Africa	General population	24	6,6, and 12	MV IRR
Kumwenda et al.[28]	2008	2003-05	787	Blantyre, Malawi	Reproductive health clinics	12	3	MV HR
Watson-Jones et al.[31]**	2009	2003-08	659	Tanzania	HSV2+ hotel/bar workers	30	3	Age-adj. HR
Reid et al.[32]	2010	2003-07	1,358	So. Africa, Zambia, Zimbabwe	HSV2+ from gen pop	18	3	MV HR
Feldblum et al.[33]	2010	2004-07	7,364	Africa & India	Microbicide trial "higher risk"	12	1	MV HR
Morrison et al. [15, 16, 25]	2010	1999-2004	6,109	Uganda, Zimbabwe, Thailand	family plan clinics	21.5	3	MSM HR
Heffron et al.[34]	2012	2004-10	3,790	7 African nations	sero-discordant. couples	12-24	3	MSM HR
Wand H, Ramjee G[35]	2012	Not reported	2,236	Durban, S. Africa	>90% from microbicide trial	Not reported	3	MV HR
Morrison et al.[36]	2012	2004-2007	5,567	South Africa	General population	9-24	3	MSM HR
McCoy [37]	2013	2003-2007	4,913	South Africa, Zimbabwe	Diaphragm/gel HIV prev. trial	24	3	MV HR
Crook et al. [38]	2014	2005-2009	8,663	S Africa, Uganda, Tanzania, Zambia	Microbicide trial sero-disc. couples	12	1	Inv. Prob. W'ted HR

*74% DMPA users; 26% used other forms of SC.
**67% DMPA users; 33% COC users.

Results

Data are presented as composites of tabular data and semi-logarithmic Forest plots for cross-sectional (Fig. 1) and longitudinal studies (Fig. 2). The combining of data from individual studies of both types, using a random effects model, produced a significantly positive cumulative point estimate of OR and HR, respectively, the latter showing a slightly stronger association (HR = 1.49; 95% CI: 1.28 – 1.73 v. OR = 1.41; 95% CI:

1.15 – 1.73). The consistency of the association between IC use and HIV acquisition is noteworthy in that out of the eight cross-sectional studies and 16 longitudinal studies, there are no outliers, i.e., the 95% CI of each study includes the pooled OR. Consistency across primary studies is also reflected by the fact that the overwhelming majority of both cross-sectional (88%) and longitudinal (75%) studies favor a positive association.

Figure 1

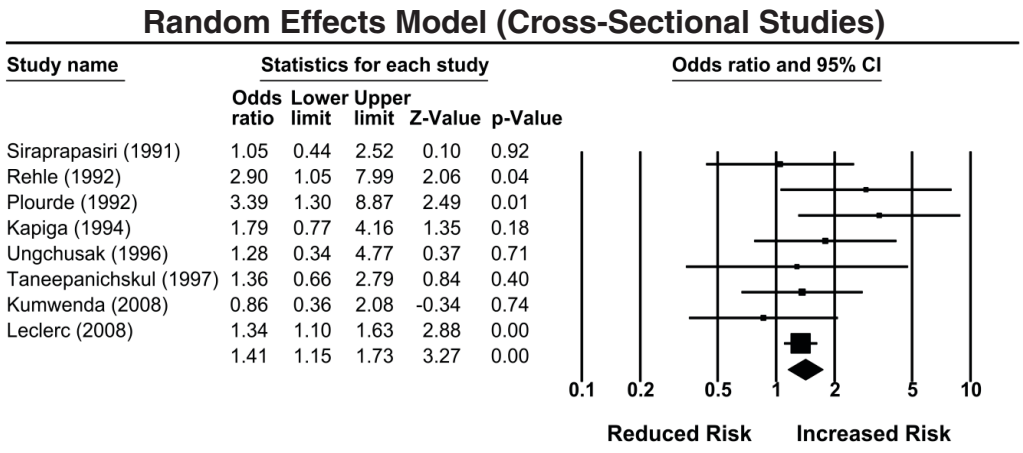
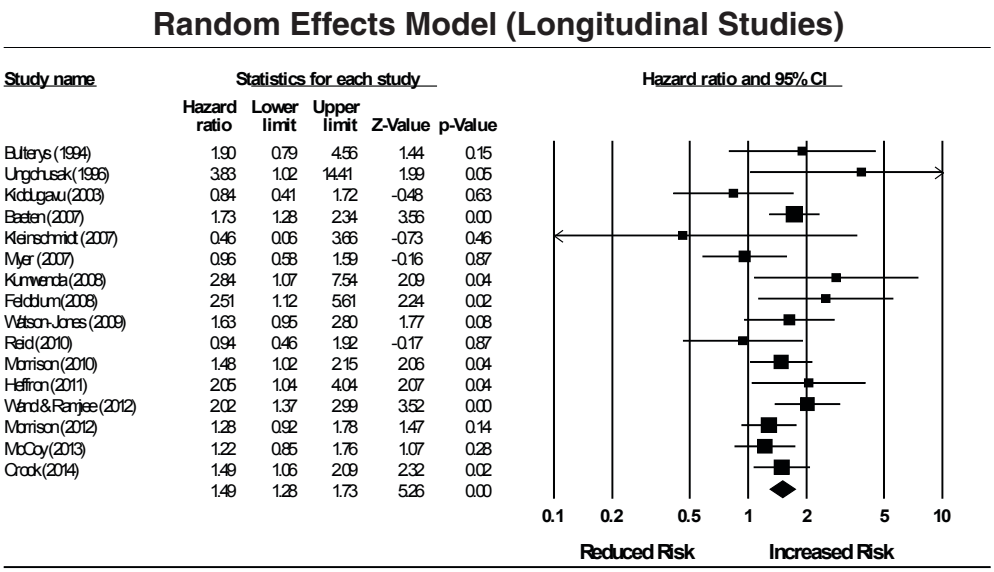


Figure 2



Discussion

Cumulatively, both cross-sectional and longitudinal studies show a significant positive association between HIV-1 positivity and IC use. However, the cross-sectional studies are considerably weaker than the longitudinal studies owing to their reporting only prevalence ORs, since the actual exposure to HIV among study participants was largely unknown. Hence, the cross-sectional studies comprise an early hint as to the potential of IC to increase HIV seroconversion rates, whereas the longitudinal studies provide a much clearer picture of the role of IC.

Importantly, the present review differs substantially from the other two meta-analyses[4,5]—both published in 2015—that examine the association between DMPA use and HIV acquisition. Morrison et al.[4] acquired and pooled individual participant data, thus including much reviously unpublished data. They also excluded several published studies whose authors did not participate in the meta-analysis or which otherwise did not meet rigorous inclusion criteria, such as having follow-up visits more than 6 months apart. Ralph et al.[5] restricted their analysis to published studies (as did we), but also used rigorous exclusion criteria such as not controlling for condom use and suffering a less than 30% loss-to follow-up. Both meta-analyses restricted inclusion to prospective studies and to subjects from sub-Saharan Africa. Hence, no data published prior to 2003 were included.

In contrast, we have made the present meta-analysis as inclusive as possible, including cross-sectional studies as well as longitudinal. Hence, we included the very earliest studies, going back to 1991.[17] Despite these substantial differences in the designs and data included in these meta-analyses, it is striking how all have come up with almost identical results.

Potential Biological Mechanisms

One of the classical effects of progesterone is immunosuppression, in terms of enabling tolerance of the presence of the fetus by the maternal immune system. Another classical effect is the luteal phase thinning of the vaginal epithelium. Evidence for both mechanisms playing a role in the consequent facilitation of disease transmission was reviewed by Wang, et al.[42] Marx et al.[43] experimentally demonstrated dramatically increased susceptibility of retroviral transmission of simian immunodeficiency virus (SIV) in Rhesus macaques (78% infection rate in progesterone-treated animals v. 10% in controls). Hence, the chronically high progestin levels that accompany use of any steroidal contraceptive, particularly injectable or implantable progestins, suggests the possibility of increasing susceptibility to HIV transmission, as Marx et al. observed in their 1999 meta-analysis of OC and HIV infection.

More recent data presented by Hujibrechts et al.,[44] however, suggest that DMPA, in addition to its progesterone agonist action, confers an additional measure of immunosuppression via agonistic interaction with the glucocorticoid receptor (GR), an effect not shared by norethisterone (whether used as the acetate—NET-A—or enanthate ester—NET-EN), for example. Thus, Hujibrechts et al. demonstrated the *in vitro* inhibition of

immune cytokine production and T-cell proliferation in the presence of MPA, as well as higher levels of surface HIV-1 coreceptors in MPA-treated T-cells, both effects occurring via GR activation. Tomasicchio et al.[45] recently demonstrated the *in vitro* facilitation of T-cell apoptosis via GR activation in the presence of contraceptive dose levels of MPA but not Net-A or physiological levels of progesterone, hence also suggesting that DMPA may facilitate the progression as well as transmission of HIV infection. Direct evidence of increased tranmission of HIV has recently been provided by Heffron et al.,[42] who demonstrated elevated HIV-1 RNA concentrations in endocervical secretions of HIV+ women using IC (mostly DMPA) v. women using OC.

Most recently, the meta-analyses of Morrison et al.[4] and Ralph[5] report similar, significant risk elevations with DMPA use (pooled HR: 1.50; 95% CI 1.24 – 1.83 and pooled HR: 1.40; 95% CI 1.16 – 1.69, respectively), but small, non-significant risk elevations for injectable NET-EN (pooled HR: 1.24; 95% CI 0.84 – 1.82 and pooled HR: 1.10; 95% CI 0.88 – 1.37, respectively) and null associations with COC use. While NET-EN data are scant, these data suggest the possibility that both NET-EN and DMPA contribute to risk by maintaining a high and constant progestin concentration, but DMPA provides its major risk increasing effect as a glucocorticoid agonist.

Potential Impact and Ethical Considerations

A remarkable finding of the present meta-analysis is the consistency of the positive association observed between DMPA use and the HIV transmission (Table 1) across many different populations in Africa and Asia, with large differences in lifestyle and sexual practices, the prevalence of other STIs such as HSV-2, and with many differences in study design, such as focusing on other outcome variables. While it must be acknowledged that the earlier studies are generally much weaker in design—especially due their cross-sectional nature—we believe that their inclusion gives a more accurate picture of the time frame during which useful information became available about the role of an elective intervention on the risk of acquiring a life-threatening infection.

We find it particularly noteworthy that the earlier, less rigorous cross-sectional studies, ignored in the other recent meta-analyses, provide almost identical findings to those of the more recent, rigorous, longitudinal studies. Indeed, it is troubling that, despite the often lethal effects of HIV infection and the even stronger association than has generally been observed with combined OC,[42] as well as the documentation of plausible mechanisms by which DMPA in particular can increase susceptibility, there has been a reluctance on the part of researchers to conclude that DMPA presents a significant hazard to women. Even as recently as 2013, Polis and Curtis tepidly concluded: "More definitive evidence for the existence and size of any potential effect could inform appropriate counseling and policy responses…."[47] Yet even greater emphasis on protecting "highly efficacious" contraception, at the expense of protecting the lives and health of the women concerned, can be found in the literature. Thus, Stephenson[48] opined that even if research "were to present a more compelling case to indicate that hormonal contraception increases the risk of HIV transmission, women could be advised that

such contraceptives do not protect against HIV and might increase susceptibility. But such advice would need to be weighed against the risks of rejecting safe and reliable contraception." Indeed, it is difficult to reconcile such a policy consideration to withhold the disclosure of the documented dangers of any elective medication for any reason, as such policy would clearly violate any reasonable standard of medical ethics and the need to obtain informed consent.

Conclusions

We conclude that the extant epidemiological literature, coupled with the documentation of plausible biological mechanisms by which DMPA has been shown to weaken both the epithelial and immunological barriers to HIV transmission, makes a compelling case that DMPA presents a substantial hazard to women of increased risk of HIV transmission from infected men to women, independent of the presence of other STIs. This result essentially confirms the findings of the two other meta-analyses examining this question. Yet it is troubling that there still seems to be a lack of urgency in providing this important knowledge to those women most exposed, DMPA being presently the most widely used form of steroidal contraception in sub-Saharan Africa.[4] Thus, Morrison et al.[4] merely "highlight the need to initiate randomized controlled trials to provide more definitive evidence of the effects of hormonal contraception, particularly DMPA, on HIV risk." Ralph et al.[5] also look forward to furthering research with a randomized trial. However, at least they acknowledge that such a trial, in light of the now documented danger of DMPA in increasing HIV acquisition risk "might violate the principle of equipoise required for a trial."[5] It seems to us that the ongoing widespread use of DMPA, without including substantial warnings to women using it about the increased HIV risk, may essentially constitute a very large scale trial that is already violative of patients' rights to give informed consent. Policymakers and practitioners should incorporate this knowledge accordingly, to ensure that a woman's right to make informed choices about her reproductive and general health is protected, and not subordinated to public policy concerns about population control.

References

[1] Wang CC, Kreiss JK, Reilly M. Risk of HIV infection in oral contraceptive pill users: a meta-analysis. *JAIDS* 1999;21:51-58.

[2] Rehle T, Brinkmann U, Siraprapasiri MT, et al. Risk factors of HIV-1 infection among female prostitutes in Khon Kaen, Northeast Thailand. *Infection* 1992;20:328-31.

[3] Polis CB, Westreich D, Balkus JE, et al. Assessing the effect of hormonal contraception on HIV acquisition in observational data: Challenges and recommended analytic approaches. *AIDS* 2013;27:s35-s43.

[4] Morrison CS, Chen P-L, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition: An individual participant data meta-analysis. *PLoS Med* 2015;12:e1001778. doi: 10.1371/journal.pmed.1001778.

[5] Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. *Lancet Infect Dis* 2015;15:181-9. doi: 10.1016/S1473-3099(14)71052-7.

[6] Nagachinta T, Duerr A, Suriyanon V, et al. Risk factors for HIV-1 transmission from HIV-seropositive male blood donors to their regular female partners in northern Thailand. *AIDS* 1997;11:1765-72.

[7] Allen S, Lindan C, Serufilira A, et al. Human immunodeficiency virus infection in urban Rwanda. *JAMA* 1991;266:1657-63.

[8] Mati JKG, Hunter DJ, Maggwa BN, et al. Contraceptive use and the risk of HIV infection in Nairobi, Kenya. *Int J Gynaecol Obstet* 1995;48:61-67.

[9] Kapiga SH, Lyamuya EF, Lwihula GK, et al. The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania. *AIDS* 1998;12:75-84.

[10] Kilmarx PH, Limpakarnjanarat K, Mastro TD, et al. HIV-1 seroconversion in a prospective study of female sex workers in northern Thailand: continued high incidence among brothel-based women. *AIDS* 1998;12:1889-98.

[11] Criniti A, Mwachari CW, Meier AS, et al. Association of hormonal contraception and HIV-seroprevalence in Nairobi, Kenya. *AIDS* 2003;17:2667-69.

[12] Chao A, Bulterys M, Musanganire F et al. Risk factors associated with prevalent HIV-1 infection among pregnant women in Rwanda. *Int J Epidemiol* 1994;23:371-80.

[13] Martin HL, Nyange PM, Richardson BA, et al. Hormonal contraception, sexually transmitted diseases, and risk of heterosexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1998;178:1053-59.

[14] Lavreys L, Baeten JM, Martin HL, et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS* 2004;18:695-97.

[15] Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and HIV acquisition. *AIDS* 2007;21:85-95.

[16] Morrison CS, Turner AN, Jones LSB, et al. Highly effective contraception and acquisition of HIV and other sexually transmitted infections. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2009;23:263-84.

[17] Siraprapasiri T, Thanprasertsuk S, Rodklay A, et al. SHORT COMMUNICATION: Risk factors for HIV among prostitutes in Chiangmai, Thailand. *AIDS* 1991;5:579-82.

[18] Ungchusak K, Rehle T. Determinants of HIV infection among female commercial sex workers in northeastern Thailand: results from a longitudinal study. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;12:500-507.

[19] Taneepanichskul S, Intaraprasert S, Phuapradit W, et al. Use of Norplant® implants in asymptomatic HIV-1 infected women. *Contraception* 1997;55:205-207.

[20] Plourde PJ, Plummer FA, Pepin J, et al. Human immunodeficiency virus type 1 infection in women attending a sexually transmitted diseases clinic in Kenya. *J Infect Dis* 1992;166:86-92.

[21] Kapiga SH, Shao JF, Lwihula GK, et al. Risk factors for HIV infection among women in Dar-es-Salaam, Tanzania. *J Acquir Immune Defic Syndr* 1994;7:301-309.

[22] Bulterys M, Chao A, Habimana, et al. Incident HIV-1 infection in a cohort of young women in Butare, Rwanda. *AIDS* 1994;8:1585-92.

[23] Baeten JM, Benki S, Chohan V, et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. *AIDS* 2007;21:1771-77.

[24] Kiddugavu M, Makumbi F, Wawer MJ, et al. Hormonal contraceptive use and HIV-1 infection in a population-based cohort in Rakai, Uganda. *AIDS* 2003;17:233-40.

[25] Morrison CS, Pai-Lien C, Cynthia K, et al. Hormonal contraception and HIV acquisition: Reanalysis using marginal structural modeling. *AIDS* 2010;24:1778-81

[26] Kleinschmidt I, Rees H, Delany S, et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception* 2007;75:461-67.

[27]. Myer L, Denny L, Wright TC, et al. Prospective study of hormonal contraception and women's risk of HIV infection in South Africa. *Int J Epidemiol* 2007;36:166-74.

[28] Kumwenda NI, Kumwenda J, Kafulafula G, et al. HIV-1 incidence among women of reproductive age in Malawi. *Int J STD AIDS* 2008;19:339-41.

[29] Kumwenda JJ, Makanani B, Taulo F, et al. Natural history and risk factors associated with early and established HIV type 1 infection among reproductive-age women in Malawi. *Clin Infect Dis* 2008;46:1913-20.

[30] Leclerc PM, Dubois-Colas N, Garenne M, et al. Hormonal contraception and HIV prevalence in four African countries. *Contraception*. 2008;77:371-76.

[31] Watson-Jones D, Baisley K, Weiss HA, et al. Risk factors for HIV incidence in women participating in an HSV suppressive treatment trial in Tanzania. *AIDS* 2009;23:415-22.

[32] Reid SE, Dai JY, Wang J, et al. Pregnancy, contraceptive use, and HIV acquisition in HPTN 039: Relevance for HIV prevention trials among African women. *J Acquir Immune Defic Syndr* 2010;53:606-13.

[33] Feldblum PJ, Lie CC, Weaver MA, et al. Baseline factors associated with incident HIV and STI in four microbicide trials. *Sex Transm Dis* 2010;37:594-601.

[34] Heffron R, Donnell d, Rees H et al. Use of hormonal contraceptives and risk of HIV-1 transmission: A prospective cohort study. *Lancet Infect Dis* 2012;12:19-26.

[35] Wand H, Ramjee G. The effects of injectable hormonal contraceptives on HIV seroconversion and on sexually transmitted infections. *AIDS* 2012;26:375-80.

[36] Morrison CS, Skoler-Karpoff S, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition among women in South Africa. *AIDS* 2012;26:497-504.

[37] McCoy SI, Zheng W, Montgomery ET, et al. Oral and injectable contraception use and risk of HIV acquisition among women in sub-Saharan Africa. *AIDS* 2013;27:1001-9.

[38] Crook AM, Ford D, Gafos M, et al. Injectable and oral contraceptives and risk of HIV acquisition in women: An analysis of data from the MDP301 trial. *Hum Reprod* 2014;29:1810-7.

[39] Hedges, L. V., & Vevea, J. L. Fixed- and random-effects models in meta-analysis. *Psych Meth* 1998;3:486-504.

[40] Hunter, J. E., & Schmidt, F. L. (2000). Fixed effects vs. random effects meta-analysis models: Implications for cumulative research knowledge. *Int J Selection Assessment* 2000;8:275-292.

[41] Spiegelman D. Determinants of HIV infection among female commercial sex workers in northeastern Thailand: Results from a longitudinal study (Erratum). *J AIDS* 1998;18:192.

[42] Wang CC, Kreiss JK, Reilly M. Risk of HIV infection in oral contraceptive pill users: a meta-analysis. *J AIDS* 1999;21:51-58.

[43] Marx PA, Spira AL, Gettie A, et al. Progesterone implants enhance HIV vaginal transmission and early virus load. *Nat Med* 1996;2:1084-1089.

[44] Huijbregts, Richard PH, et al. Hormonal contraception and HIV-1 infection: Medroxyprogesterone acetate suppresses innate and adaptive immune mechanisms. *Endocrinol* 2013;8:1282-1295.

[45] Tomasicchio, Michele, et al. The Progestin-Only Contraceptive Medroxyprogesterone Acetate, but Not Norethisterone Acetate, Enhances HIV-1 Vpr-Mediated Apoptosis in Human CD4+ T Cells through the Glucocorticoid Receptor. *PloS one* 2013:8 e62895.

[46] Heffron R, Donnell d, Rees H *et al*. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012;12:19-26.

[47] Polis, Curtis KM, Phillipes SJ, Chelsea B. Hormonal contraceptive use and female-to-male HIV transmission: a systematic review of the epidemiologic evidence. *AIDS* 2013;27: 493-505.

[48] Stephenson JM. Systematic review of hormonal contraception and risk of HIV transmission: When to resist meta-analysis. *AIDS* 1998;12:545-553.

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Induced Abortion and Breast Cancer

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Biology of the Abortion Breast Cancer Link

The basic human biology of breast maturation through pregnancy is the basis of the abortion breast cancer link. The protective effect of a full-term pregnancy on breast cancer risk has been known since the Middle Ages when it was noted that nuns had a higher risk of breast cancer than women with children.

Since 1976, there has been a 400% increase risk of in-situ breast cancer in women under 50 by SEER data. There has been a 2% per year increase in metastatic breast cancer in women under 40. Why? An understanding of the biological basis of breast cancer risks makes it possible to understand, predict and minimize those risk factors which will affect a woman's future risk of breast cancer.

Medical authorities agree:

- That a full-term pregnancy lowers a woman's risk of breast cancer.[1]
- That each additional pregnancy further lowers her risk by 10%.[2]
- That for each year after age 20, a woman who delays a full-term pregnancy, increases her risk of premenopausal breast cancer by 5% and postmenopausal breast cancer by 3%.[3]

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[1] Mats Lambe, "Chapter Six: Reproductive Factors," in *Breast Cancer Epidemiology*, ed. Christopher I. Li (New York: Springer, 2009), 129-136; Lambe M, Hsieh CC, Chan HW, et al. "Parity, age at first and last birth, and risk of breast cancer. A population-based study" in *Sweden Breast Cancer Res Treat* 38:305-311, 1996.

[2] Mats Lambe, Chung-cheng Hsieh, Hsiao-wei Chan, Anders Ekbom, Dimitrios Trichopoulos, and Hans-Olov Adami, "Parity, Age at First and Last Birth, and Risk of Breast Cancer: A Population-Based Study in Sweden," *Breast Cancer Research and Treatment* 38 (1996): 305-311.

[3] Françoise Clavel-Chapelon and Mariette Gerber, "Reproductive Factors and Breast Cancer Risk," *Breast Cancer Research and Treatment* 72, no. 2 (2002): 107-115.

- That induced abortion increases the risk of premature birth which in turn increases breast cancer risk if it occurs before 32 weeks.[4]

These 4 medical facts necessarily cause a pregnant woman who chooses to end her pregnancy by abortion, to increase her risk of Breast cancer.

In practical terms, this is the situation: A woman has an unplanned pregnancy. If she chooses to continue her pregnancy and has a full-term pregnancy, or one that lasts at least 32 weeks, she will lower her risk of breast cancer.

OR

If she chooses to end her pregnancy with an induced abortion, she will necessarily have an increased risk of breast cancer because:

- She will lose the benefit of a full-term pregnancy.
- She will delay a full-term pregnancy or have no or fewer full-term pregnancies.
- She may have a premature delivery before 32 weeks of another pregnancy.

Biological Basis of Breast Cancer Risk

Inherited genes or genes mutated after birth account for approximately 6-10% of all breast cancers (e.g. inherited BRCA genes 1& 2 or radiation, virus or chemically induced injury). Approximately 90% factors that influence the rate of breast cancer are due to the interplay of two influences: 1) cumulative lifetime exposure to estrogen and 2) amount and timing of breast lobular cell differentiation from Type 1 lobules, the most primitive type to Type 4 lobules, the most differentiated.

It is the biology of the breast lobule maturation that occurs during pregnancy which accounts for the abortion breast cancer link. At full development, the breast is comprised of 15-25 lobes which are in turn comprised of lobules. Lobules in turn are composed of breast cells.

There are 4 types of lobules whose structural differences appear under the microscope.[5] Type 1, 2 & 3 lobules are differentiated by the average number of ductules per lobular unit: (Type 1 has 11; Type 2 has 47; Type 3 has 80). Type 4 lobules are fully matured and contain colostrum or milk.

These 4 types of lobules are also metabolically different with different breast cancer potential. Type 1 & 2 lobules have more estrogen and progesterone receptors than Type 3.[6] Type 1 and 2 lobules grow through mitosis (cell division) when estrogen and proges-

[4] P. Shah and J. Zao, on behalf of Knowledge Synthesis Group of Determinants of Preterm/LBW Births, "Induced Termination of Pregnancy and Low Birthweight and Preterm Birth: A Systematic Review and Meta-Analyses," *British Journal of Obstetrics and Gynaecology* 116, no. 11 (2009): 1425-1442; Hanes M. Swingle, Tarah T. Colaizy, M. Bridget Zimmerman, and Frank H. Morris, "Abortion and Risk of Subsequent Preterm Birth: A Systematic Review and Meta-Analyses," *Journal of Reproductive Medicine* 54 (2009): 95-108.

[5] Jose Russo, Yun-Fu Hu, Xiaoqi Yang, Irma Russo, "Chapter 1: Developmental, Cellular, and Molecular Basis of Human Breast Cancer," *Journal of the National Cancer Institute Monographs No.*27 2000;27:17-37; Russo J et al Biology of Disease, "Comparative study of Human and Rat Mammary Tumorigenesis." *Laboratory Investigation* Vol 62, No 3 pages 244-278.

[6] Jose Russo, Yun-Fu Hu, Xiaoqi Yang, Irma Russo, "Chapter 1: Developmental, Cellular, and Molecular Basis of Human Breast Cancer," *Journal of the National Cancer Institute Monographs No.*27 2000;27:17-37.

terone levels are elevated. Mitosis requires replication of DNA (genes) and therefore can result in mutations. Mutated cells also undergo mitosis. Multiple mutations can cause cancer cells to form. Cells of Type 1 & 2 lobules also multiply faster than Type 3 resulting in more chances for mutations to occur. This growth (proliferation) under estrogen and progesterone stimulation explains the cancer causing properties of estrogen/progestin combination drugs.

Type 1 lobules mature into Type 2 lobules under the cyclic influence of the female hormones, estrogen and progesterone, during menstrual cycles. Type 2 lobules only become fully mature into Type 4 lobules under the influence of the hormonal changes of a full-term pregnancy. Type 4 regress to Type 3 after weaning. Human Placental Lactogen (hPL) made by the fetal-placental unit during pregnancy in concert with other hormones induces full differentiation of Type 2 breast tissue to Type 4 lobules, which are cancer resistant. When Type 4 lobules regress to Type 3 post-weaning, Type 3 lobules are cancer resistant.

In addition to the protection provided by terminal differentiation under the influence of hPL produced by the placenta, another pregnancy hormone, Human Chorionic Gonadotropin (hCG) stimulates the ovary to produce inhibin, a cancer suppressing hormone, increasing the protection of the mother from carcinogenic stimuli even more. **During the first half of pregnancy, the proliferation phase, Type 1 and Type 2 lobules increase in number.** By week 20 of a 40-week (full-term) pregnancy, the breast has doubled in volume. The number of lobules in the breast increase through a decrease in the amount of breast stroma, or connective tissue, around the lobules.[7]

But, when the pregnancy ends prior to 32 weeks, the breast is arrested in a state of predominantly Type 1 and 2 lobules. This arrest occurs whether the pregnancy ends with a live birth (delivery) or the birth of a dead fetus (abortion). The longer the pregnancy proceeds before the abortion or preterm delivery prior to 32 weeks, the greater the number of undifferentiated lobules are left and the higher the risk. (Melbye's 1997 and Daling's 1994 studies). Premature births before 32 weeks more than doubled the risk of breast cancer due to the fact that the breast tissue has not gone through differentiation into Type 3 & 4 lobules.

Timing of First Full Term Pregnancy

The longer a woman waits before having her first child, the higher her risk because she has a longer "susceptibility window."[8] For example, a woman who gives birth at 18 has a 50-75% lower risk of breast cancer than a woman who waits until she is 30. There is a 5% per year increase in pre-menopausal breast cancer for each year that a pregnancy is delayed beyond age 20. The protective effect of a full-term pregnancy on breast cancer risk has been known since the Middle Ages when it was noted that nuns had a higher

[7] Jose Russo and Irma H. Russo, "Development of the Human Mammary Gland," in *The Mammary Gland,* eds. M. Neville and C. Daniel (New York: Plenum Publishing Corporation, 1987).

[8] F.M. Biro and M.S. Wolff, Chapter 2: "Puberty as a Window of Susceptibility," in *Environment and Breast Cancer*, ed. J. Russo (New York: Springer, 2011), 29-36.

risk of breast cancer than women with children.[9] A full term pregnancy also reduces the number of stem cells in the breast where cancers can start.[10] For women who have delayed childbearing and thus have a long susceptibility window, the first pregnancy transiently increases her breast cancer risk, then subsequently decreases the risk.[11]

Four Factors Determining Breast Cancer Risk

Delay in childbearing is not the only reproductive factor to affect breast cancer risk. Breast cancer risk is affected by the interplay of four factors:

- Hormonal methods of fertility regulation
- Menstrual cycle patterns
- Breast maturational stage and
- Pregnancy Outcomes

1. Hormonal Methods of Fertility Regulation

- Main Point: All hormone-based fertility control methods increase breast cancer risk
- Continuous combined hormones ("Birth Control Pills"), hormonal injections (Depo-Provera), hormonal implants (Norplant), hormonal contraceptives given by intravaginal, intrauterine (IUD) or transdermal (patch) routes
- Fertility drugs to induce ovulation or "super-ovulation" as in donor egg cycles (Clomid, Perganol)
- Abortion inducing hormonal drugs (Morning-after pill, IUD, Ella?)

2. Menstrual Cycle Patterns

- Main Point: The more regular ovulatory cycles a woman has, the higher her risk of breast cancer. The longer the time it takes to develop regular ovulatory cycles, the lower her risk of breast cancer. That is because anovulation results in fewer cycles have lower estrogen and less stimulation of the breast tissue Factors affecting risk include:
- Number of lifetime cycles (age at menarche, age at menopause)
- Number of anovulatory cycles
- Length of time to develop regular cycles post menarche

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[9] Bernardino Ramazzini with J. Corona, De morbis artificum diatriba (Venice, 1743), as cited in Mats Lambe, "Reproductive Factors," in *Breast Cancer Epidemiology*, ed. Christopher E. Li (Springer, 2009), 120.

[10] S. Choudhury et al., "Molecular Profiling of Human Mammary Gland Links Breast Cancer Risk to a p27(+) Cell Population with Progenitor Characteristics," *Cell Stem Cell* 13 (2013): 117-130.

[11] Note that women who delay first birth until age 25 or later have, relative to nulliparous women, a marginally statistically significantly increased risk of diagnosis at age 30. *See* Mats Lambe, Chung-cheng Hseih, Dimitrios Trichopoulos, Anders Ekbom, Maria Pavia, and Hans-Olov Adami, "Transient increase in the risk of breast cancer after giving birth," *New England Journal of Medicine* 331 (1994): 5-

3. Breast Maturation

- Main Point: Maturation of the majority of the breast tissue from type 1 and 2 lobules to cancer resistant type 4 lobules requires a pregnancy with duration lasting over 32 weeks.

4. Pregnancy Outcomes

A. Normal Pregnancies

- Main Point: The earlier in life a woman has a pregnancy lasting over 32 weeks, the lower her risk of breast cancer.
- Each additional child lowers her breast cancer risk further. Each birth results in a 10% risk reduction.
- Breast feeding further reduces the risk, depending on the cumulative length of lactation.
- Each year a woman delays term pregnancy after age 20 increases her risk of premenopausal breast cancer by 5% per year, and increases her risk of post-menopausal breast cancer by 3% per year.
- Stem Cell Paradigm: Parity induces changes in stem cells to produce a cancer resistance stem cell that has implications in drug therapies directed against stem cells to prevent recurrences.

B. Adverse Pregnancy Outcomes

- Main Point: Pregnancy hormones stimulate a proliferation of Type 1 and 2 lobules in the first half of pregnancy. The majority of the breast tissue does not reach terminal differentiation to Type 4 lobules until after 32 weeks gestation. Thus, ending a pregnancy prior to 32 weeks arrests the majority of breast tissue in a state susceptible to malignant transformation.
- spontaneous abortions:
  - first trimester (prior to 12 weeks) no increased risk;
  - second trimester (after 12 weeks) increased risk, with risk increasing as gestational age increases.
- Induced abortions:
  - first trimester increased risk
  - second trimester increased risk
- Stillbirths after 32 weeks no increased risk
- Ectopic pregnancies: no data, but would expect early ectopics to mimic hormone pattern of first trimester miscarriages.
- Pre term delivery (24-31 weeks) increased risk

Summary of Reproductive Risk Factors[12]

Premature births before 32 weeks more than doubled the risk of breast cancer. The breast tissue has not gone through differentiation into Type 3 & 4 lobules, which are cancer resistant AND the amount of breast tissue has doubled in volume so there are more places for cancers to start. Before 32 weeks, the majority of the breast tissue has not undergone terminal differentiation into Type 4 lobules, but arrests in the immature Type 1 and Type 2 lobular state. The longer the pregnancy proceeds before abortion, the greater the number of undifferentiated lobules are left and the higher the risk. (Melbye's 1997 and Daling's 1994 studies) This interruption of pregnancy before 32 weeks can be from a preterm birth resulting in a live baby, or from an abortion, resulting in a dead baby. The breast differentiation is affected by the hormonal milieu of the stage of pregnancy, so second trimester abortions and preterm births result in similar increases in breast cancer risk. This increase in breast cancer risk with interrupted pregnancies is also seen in first trimester induced abortions, but not first trimester miscarriages. That is because first trimester miscarriages do not produce sufficient estrogen to induce proliferation because the embryo/fetus does not produce enough hCG to stimulate the breast or the mother's ovaries don't produce enough estrogen & progesterone to sustain a pregnancy, whereas second trimester abortions are associated with sufficient estrogen production.

A secondary effect of induced abortion is that there may be injury to the cervix which renders it incompetent and results in a premature birth; if that birth is before 32 weeks it will double breast cancer risk.

World-wide Abortion Breast Cancer Link Studies[13]

In 1964, the US Surgeon General applied the newly developed Bradford Hill criteria for causality to the cigarette lung cancer link epidemiologic studies to warn the public. These same criteria have been fulfilled by the world's epidemiologic studies of the abortion breast cancer link. From 1957 to 2013 there are 73 studies and 3 meta-analyses differentiating induced from spontaneous abortion. Fifty-seven studies show a positive association and 34 studies are statistically significant to the 95th percentile.

Bradford Hill Causality Guidelines and the Association Between Abortion and Breast Cancer

Dr. Hill developed nine criteria for drawing a causal inference from an epidemiologic association, which were first applied to smoking and preterm birth. These nine criteria are:

1. Strength (of association)
2. Consistency

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[12] Lanfranchi, AE, and Fagan, P, "Breast Cancer and Induced Abortion: A Comprehensive Review of Breast Development and Pathophysiology, the Epidemiologic Literature, and Proposal for Creation of Databanks to Elucidate All Breast Cancer Risk Factors," *Issues in Law & Medicine,* Volume 29, Number 1, (2014) 3-133.

[13] *Id.*

3. Specificity (of cause)
4. Temporality
5. Biological gradient (i.e., a dose effect)
6. Plausibility
7. Coherence
8. Experiment
9. [By] analogy

Examining each of these criteria with regards to abortion and breast cancer is illuminating.

1. *Strength (of association):* ***The strength of the association between the two factors can be indicative of a causal association. At least a 200% increase in risk is needed, which means a : Relative Risk(RR) > 3.***
   1994 Daling Study for the subgroups of teens and those with a family history of breast cancer demonstrated a RR of 8 (risks of 800% and higher).
2. *Consistency:* …an observed relationship between two factors should be made with some consistency.
   57/73 studies worldwide and 20/23 studies in the US have a positive correlation between abortion and breast cancer 31 of the worldwide and US studies are statistically significant.
3. *Specificity (of cause):* Specificity of cause—"one-to-one relationships," …is rare. Where it occurs, it may imply causality…that "diseases may have more than one cause." (e.g. asbestosis and mesothelioma)
   Carroll's 2007 study showed the greatest predictor of breast cancer incidence in 9 European countries was their abortion rates.
   Breast cancer is an hormonally driven cancer: the more estrogen a woman is exposed to in her lifetime, the higher her risk;
   Women who are pregnant are exposed to high levels of estrogen (in the presence of progesterone) causing rapid breast cell proliferation; However an induced abortion before 32 weeks does not allow for the cancer reducing effects of cellular maturation of lobules to occur thereby raising her risk by leaving more cancer vulnerable lobules exposed to more carcinogenic estrogen metabolites and genetic mutations errors caused by rapid cell division during proliferation.
4. *Temporality:* The hypothesized cause must precede the outcome.
   Breast cancers caused by abortion are found after 10 to 14 years post abortion. Average breast cancer cell doubling time takes 8 to10 years to be clinically detectable at 1cm diameter.
5. *Biological gradient (i.e., a dose effect):* If a factor is causal of a disease, then (based on biological mechanisms) increased exposure to that factor ought to increase one's risk of the disease.
   The longer the pregnancy before abortion the higher the risk and the more abortions the higher the risk. 1994 Daling Study,1997 Melbye Study.

6. *Plausibility:* The biological mechanism that explains the reason for the risk association ought to be plausible, depending upon the biological knowledge of the day.
Elevated estrogen levels in pregnancy leaves the breast with increased numbers of Type 1 and 2 lobules where cancers form without the benefit of full maturation to cancer resistant Type 4 lobules after 32 weeks.
7. *Coherence:* The hypothesis, when proven, should not do violence to related sets of scientific findings but fit in with them.
The known biology which explains the development of mature cancer resistant breast tissue during a pregnancy lasting greater than 32 weeks is consistent with the explanation of why an induced abortion before 32 weeks would increase breast cancer risk; A woman is left with MORE CELLS where breast cancers start. The same biology explains why a full term pregnancy lowers risk, why remaining nulliparous (childless) would increase risk, why having a long susceptibility window would increase risk, why having exposure to carcinogens before a full term pregnancy would increase risk more than being exposed to the same risk after a full term pregnancy.
8. *Experiment:* …experimental evidence of the relationship between a potential risk factor and a disease is sometimes possible to obtain, and it may show "the strongest support for the causation hypothesis."
A 1980 Russo and Russo study on virgin, aborted and parous rats revealed that exposure to the carcinogen DMBA caused more breast cancers in rats that had been aborted than those rats who were virginal or parous. One parous group had no cancers form after being given DMBA.
9. *[By] analogy:* Similar exposures may result in similar effects.
Premature delivery before 32 weeks doubles breast cancer risk because it leaves the breast with more places for cancers to start. In the same way induced abortion leaves the breast with more places for cancers to start.

Biases Common in Studies of the Induced Abortion-Breast Cancer Link

1. *Incomplete Questionnaires, Low User Response, and Unsuitable Circumstances for Obtaining Data:*

In one large study, over half of respondents did not completely answer the study's question on abortion history. Some answered regarding spontaneous but not induced abortion; some answered about induced but not spontaneous abortions. The authors just filled in the blank halves of their responses with "no."

2. *Health Bias or Survivor Bias:*

Many studies assessing women with breast cancer intentionally exclude women with in situ breast cancer or a previous history of breast cancer. The exclusion of women who have suffered (and perhaps died) from the disease of interest, intro-

duces health bias or survivor bias into the study, and it may artificially shrink the demonstrated effect of induced abortion on breast cancer risk.

3. ***Incorrect Time Frames:***

It takes an average of eight to 10 years for a breast cancer cell to become clinically detectable.

Many studies fail to account for this and do not follow women long enough after induced abortions or establish the right time frames for analyzing the relationship between induced abortion and breast cancer.

4. ***Unsophisticated Analysis:***

The circumstances of an induced abortion determine the extent of its influence on breast cancer risk:

- The number of abortions procured
- The parity status at the time of an induced abortion
- The age at which a woman procures an abortion
- The gestational stage at which it occurs

5. ***Unsuitable Comparisons:***

It is essential that correct reference groups are established. Aborting women and nulliparous women must be compared to parous women with no abortion history.

Governmental Filters to Accurate Abortion Information: 2003 NCI Workshop on Early Reproductive Events and Breast Cancer

One hundred scientists, save one dissenter, concluded abortion is not a risk factor for breast cancer. Note that the format was tightly controlled, and the attendees tightly controlled. The accepted association between premature birth causing increased breast cancer risk is called "epidemiologic gap." This meeting did not settle the issue from a scientific standpoint, because the actual science was not addressed.

Despite efforts to downplay or ignore the association between abortion and breast cancer, mounting evidence reveals the association, which is consistent with known breast physiology, and with multiple studies.

> The old adage "there is strength in numbers" is not always true, especially when it comes to science. Science is not advanced through polls or consensus. Observation and experimental evidence is what matters. Thankfully, being in the minority does not necessarily mean one is wrong. Case in point: The book *Hundert Autoren Gegen Einstein* (A Hundred Authors Against Einstein), a collection of various criticisms of Einstein's theory of relativity….When asked about the book, Einstein retorted by saying "Why 100 authors? If I were wrong, then one would have been enough![14]

[14] http://weeklysciencequiz.blogspot.com/2013/01/a-hundred-authors-against-einstein.html.

Abortion and Breast Cancer: Recent Evidence Confirms a Robust Link

Joel Brind, Ph.D.*

Published evidence of a link between induced abortion and future breast cancer risk dates back to 1957, when a nation-wide study in Japan showed that women with breast cancer had had 3 times as many pregnancies that ended in induced abortion, compared to normal controls.[1]

That was even before the days when the term "relative risk" was introduced (in 1959), with the typical relative risk estimate being based on the odds ratio (OR) in case-control studies. Relative risk describes numerically the relative likelihood of having a given disease—such as breast cancer—if one has had a particular exposure—such as induced abortion– compared to those who have not had the exposure.

RR 1.0 – there is no increase or decrease in risk

RR 1.5 – there is a 50% increase in risk

RR 2.0 – there is a 100% increase in risk

RR 0.5 – there is a 50% decrease in risk

In recent years, the abortion-breast cancer link became big news with the 1994 paper by Janet Daling, et al. in the *Journal of the National Cancer Institute*, which reported a statistically significant, 50% risk increase with induced abortion.[2] In results, Daling stated "Among women who had been pregnant at least once, the risk of breast cancer in those who had experienced an induced abortion was 50% higher than among other women."

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[1] M. Segi, I. Fukushima, S. Fujisaku, M. Kurihara, S. Saito, K. Asano and M. Kamoi, An Epidemiological Study on Cancer in Japan, The Report of the Committee for Epidemiological Study on Cancer, Sponsored by the Ministry of Welfare and Public Health *GANN* 1957;48(suppl.):1-63.

[2] Daling JR, Malone KE, Voigt LF, White E, Weiss NS. Risk of Breast Cancer Among Young Women: Relationship to Induced Abortion. *J Nat'l Cancer Inst.* 1994;86:1584-92.

The Daling study, however, was immediately attacked by Lynn Rosenberg in the very same issue of the JNCI, on the basis of putative reporting bias (aka response bias), since the Daling study design was retrospective (as most are). Hence, the ABC link faded quickly from the news cycle.[3]

As evidence of reporting bias, Rosenberg cited the 1991 study by Lindefors–Harris et al., which had compared the interview responses of breast cancer patients v. controls with the computerized records of abortion. The authors claimed that women with breast cancer were prone to significant "overreporting" of abortions that were not on the computerized record.[4] However, as the Lindefors–Harris group (headed by Olav Meirik) was later forced to concede, their computerized records were clearly deficient, thus implicitly retracting the preposterous idea of over-reporting (making up abortions that had never taken place).[5] In their 1998 letter to the editor, Meirik et al state: "We are not surprised to find some Swedish women confidentially reporting having had induced abortions during the period 1966-1974 that are not recorded as legally induced abortions."

Nevertheless, the concept of reporting bias continues to be falsely relied upon by those who deny the ABC link, as if it were established fact, in the same way as "Hands up! Don't shoot!" is falsely attributed to Michael Brown in Ferguson, MO. In short: Facts don't matter when the political agenda of the gatekeepers of public knowledge would have the facts be other than they are.

The ABC link next made big news when a meta-analysis of extant worldwide studies I had conducted with colleagues from Penn State Medical College, was published by the British Medical Association.[6] We reported a statistically significant OR of 1.3 among all 23 studies published.

Within 3 months of the publication of our meta-analysis, a huge prospective study by Mads Melbye et al. on women in Denmark (using US tax dollars) was published in the *New England Journal of Medicine*.[7] Melbye's conclusions: "Induced abortions have no overall effect on the risk of breast cancer." The Melbye study was widely cited as the disproof of the ABC link, because it was based on prospective computer registry data (and therefore immune to reporting bias), involved so many women (1.5 million), so many abortions (over 400,000) and so many cases of breast cancer (over 10,000).

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[3] Rosenberg L. Induced Abortion and Breast Cancer: More Scientific Data are Needed (Ed.) *J Nat'l Cancer Inst.* 1994;86:1569.

[4] Lindefors-Harris B, Eklund G, Adami H, Meirik O. Response Bias in a Case-Control Study: Analysis Utilizing Comparative Data Concerning Legal Abortions from Two Independent Swedish Studies. *Am J Epidemiol* 1991;134:1003-8.

[5] Meirik O, Adami H, Ecklund G Relations between induced abortion and breast cancer (letter to the editor) *J Epidemiol Community Health* 1998;52:209-212.

[6] Joel Brind, Vernon M Chinchilli, Walter B Severs, Joan Summy-Long Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis. *Journal of Epidemiology and Community Health* 1996;50:481-496.

[7] Melby M, Wohlfahrt J, Olsen JH, Fisch M, Wetergaard T, Helweg-Larsen K, Anderson PK. Induced Abortion and the Risk of Breast Cancer. *NEJM* 1997;336 (2):81-85.

Hence, the statistical confidence interval of the reported overall relative risk of 1.00 was extremely narrow.

However, the Melbye study was rife with flaws; in fact, flagrant violations of the scientific method. To name just two: First, it falsely claimed that abortion had been legalized in Denmark in 1973, when it had in fact been legalized in 1939. In the article, Melbye states: "In 1973, the legal right to an induced abortion through 12 weeks gestation was established for women with residence in Denmark… The induced abortions included in this anaylasis (were) those occurring between 1973 and 1992." Hence, the computerized records of abortion that were used in the calculations showed no abortions at all until 1973, although the study included all Danish women born between 1935 and 1978. It therefore included some 60,000 women who had had some 80,000 legally induced abortions before 1973, but these women were misclassified in the study as not having had any abortions.

The second obvious flaw in the Melbye study regarded the misuse of registries. "Follow-up for breast cancer for all the women began on April 1, 1968 or on their 12th birthday, whichever came later." Even though abortion records that were used in the Melbye study dated back only to 1973, they used a breast cancer registry that dated back to 1968, thus violating the most fundamental scientific rule of temporality (Cause must precede effect).

The ensuing decade (1997 – 2008) saw the publication in high-impact journals of about a dozen studies from around the Western world, which reported a null association between abortion and breast cancer. Because these studies were prospective in nature, they were touted as proving the non-existence of the ABC link because they were immune to response bias. None will be mentioned in this brief presentation, however I have previously reported on the host of flagrant methodological violations employed to arrive at a null result. Most of these data were summarized by Valerie Beral et al. in the 2004 "collaborative reanalysis" on abortion and breast cancer, published in the *Lancet*.[8]

When Beral's overall results are viewed, it is clear that most of the significantly positive studies were excluded. They were in fact excluded for a host of non-scientific reasons, such as being unable to locate original study authors, or the authors declining to participate because they believed their published data (showing a positive association) to be unreliable (even though they never retracted them).

So pervasive are the distortions of method and data in these null ABC link studies and the Beral reanalysis, that I am not shy about referring to them as fraudulent. Tellingly, a year later (2005) a study published in Science called "Scientists behaving badly" by Brian Martinson, et al.,[9] documented a shocking trend in NIH-funded research: By mid-career, more than one in five NIH-funded scientists actually admitted

[8] Beral V Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83000 women with breast cancer from 16 countries. *Lancet* 2004;363:1007-16

[9] Martinson BC, Anderson MS, deVries R. Scientists Behaving Badly. *Nature*. 2005 Jun 9;435(7043):737-38.

(anonymously) to "Changing the design, methodology or results of a study in response to pressure from a funding source."

In late 2013 (first published online, published in print in 2014), a meta-analysis by Yubei Huang et al.[10] on 36 studies from mainland China (34 of them published in the 21st Century) essentially confirmed the results we had obtained on worldwide data in our 1996 meta-analysis, i.e., a statistically significant risk increase (OR = 1.44 overall) with abortion. The Huang study also added credibility to the ABC link in that it also demonstrated a significant dose effect, as stated in their conclusions: "IA (induced abortion) is significantly associated with an increased risk of breast cancer among Chinese females, and the risk of breast cancer increases as the number of IA increases. If IA were confirmed as a risk factor for breast cancer, high rates of IA in China may contribute to increasing breast cancer rates."

But even more than that, the Huang study confirmed our explanation, published in 2004,[11] of null associations observed in the series of studies from Shanghai, China, on the basis of the fact that the high prevalence (>50%) of abortion among the general population masks the effect of abortion. This is because, when abortion is the rule rather than the exception, the women with no abortions become a minority sub-group at elevated risk due to the very reasons—sub fertility, late age at first pregnancy or nulliparity—they were not exposed to abortion. Huang et al. graphically documented this trend in the Chinese studies by means of a meta-regression analysis.

We can then extend Huang's meta-regression analysis to other of the small minority of studies reporting null or negative associations, in addition to the ones originally included in the Huang meta-analysis. Specifically, we can see that the null association reported in a 2014 study on Shanghai women by Wu et al, and the significantly negative associations reported in Yugoslavia in 1979 and Serbia in 2013, (wherein the reported prevalence among normal controls was 68%, 75% and 80%, respectively) actually fit perfectly on the Huang meta-regression line (Figure 6 in the Huang study).

Despite the strong confirmation of the reality of the ABC link in the recent Chinese studies, mainstream authorities (such as the NCI) continue to use the reporting bias argument to dismiss the findings, on the basis that the studies are almost entirely retrospective in nature. However, such biases as reporting bias have theoretical credibility only when the association is relatively weak. The worldwide overall association we reported in 1996 (OR = 1.3) and the overall association among Chinese women reported by Huang in 2014 (OR = 1.44) are weak associations. In the West, the weakness of the association (assuming the causal hypothesis is correct) is attributable to the fact that in the West, there are many risk factors for breast cancer, including nulliparity, oligoparity,

[10] Huang Y, Zhang X, Li W, Song F, Dai H, Wang J, Gao Y, Liu X, Chen C, Yan Y, Wang Y, Chen K. A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females. *Cancer Causes Control* 2014 Feb;25(2):227-36. doi: 10.1007/s10552-013-0325-7. Epub 2013 Nov 24.

[11] Brind J, Chinchilli VM Breast Cancer and Induced Abortions in China (letter to the editor) *Br J Cancer* 2004;90:2244-46.

late age at FFTP, contraceptive steroid use, alcohol use and adolescent cigarette smoking. In China, the infamous "one child policy" necessarily restricts parity in particular.

But most recently has come a flood of studies from places where, outside of abortion, there is not much to cause breast cancer. Thus we now see—in some 13 studies from the Indian subcontinent since 2008 alone—very strong associations between abortion and breast cancer—averaging OR>4. So for example, we see that, on both sides of the border between India and Bangladesh, the ABC link has no respect for this fortified international boundary: A 2014 study of Hindu women from West Bengal (India) reported an OR = 10.66,[12] and a 2013 study[13] of Muslim women from East Bengal (Bangladesh) reported an OR = 20.62 for abortion and breast cancer. These strong associations are attributable to the fact that traditionally, women from this region almost all marry and start having children in their teens, never smoke, never drink alcohol, etc. In short, there isn't much else in the way of exposure that can cause breast cancer besides abortion (and contraceptive steroids, also strongly associated with breast cancer in these women). Hence, the ABC link stands out like a proverbial sore thumb in these populations, and cements the conclusion that the ABC link is real and causal in nature (along with all the supporting biological evidence, of course.)

Conclusions:

1. New evidence of the ABC link published in 2014 includes:
   a) A meta-analysis of 36 studies in China, showing an average risk increase of 44% among women who've had any abortions.
   b) Since 2008 alone, at least 13 studies in South Asia (10 in India; one each Pakistan, Bangladesh and Sri Lanka) have appeared, all showing increased risk; ave. OR>4; two with OR>10.
2. The Chinese meta-analysis not only reinforces the reality of the ABC link, but also the evidence and epidemiological basis for the link's being masked by high prevalence of induced abortion in the general population of countries like China and Serbia, where abortion is used as birth control to limit family size.
3. The strong associations reported from the Indian sub-continent further reinforce the reality of the ABC link, knocking out even the plausibility of explanations such as reporting bias.
4. The new studies from Asia are chilling in their implication:
   Literally millions of women will likely die of breast cancer in India and China alone because they had an abortion.

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[12] Roy AG, Purkait P, Barman M, Sarkar B, Bandyopadhyay AR Association of lifestyle variables with the novel mutation of BRCa1 gene in breast cancer: a case-control study among the Bengalee Hindu females of West Bengal, India. *W J of Pharmacy and Pharmaceutical Sciences* 2014;3 (6):1213-1226.

[13] Jabeen S, Haque M, Islam J, Hossain MZ, Begum A, Kashem MA Breast cancer and some epidemiological factors: A hospital based study. *J Dhaka Med Coll* 2013; 22 (1):61-66.

The Use of Isomolecular Progesterone in the Support of Pregnancy and Fetal Safety

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Introduction

Progesterone support in pregnancy has been in use for over 60 years, having received its start in the 1940s. Its initial use was in patients who had habitual spontaneous abortion caused by luteal phase deficiency. More recently, the administration of progesterone later in pregnancy has been considered to be justified because of an observed decrease in circulating progesterone with the onset of labor,[1] an association of premature labor with decreased progesterone concentrations,[2] and the observation that progesterone has a tocolytic effect.[3]

A considerable boost to the use of progestational agents to reduce preterm delivery was received with the publication of two papers which showed a sigificant reduction in preterm delivery rates with the prophylactic administration of either progesterone or 17-*a* hydroxyprogesterone caproate. Recently it has been shown, however, that its use is not universal.[4] This may be related to the significant late sequelae that were documented following the *in utero* exposure of the fetus to the potent steroid diethylstilbestrol (DES) and that this bad experience cast "a long shadow,"[5] In spite of this, the use of proges-

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[1] Turnbull A, Patten P, Flynt A, Keirse J, Jeremy J, Anderson A: Significant Fall in Progesterone and Rise in Estradiol Levels in Human Peripheral Plasma Before Onset of Labor. *Lancet* 1974; i:101.

[2] Csapo A, Pohanka O, Kaihola H: Progesterone Deficiency and Premature Labour. *Br Med J* 1974; i:137.

[3] Ferre F, Usan M, Janssen SY: Oral Administration of Micronized Natural Progesterone in Late Human Pregnancy: Effects on Progesterone and Estrogen Concentrations in the Plasma, Placenta and Myometrium. *Am J Obset Gynec* 1985; 148:26.

[4] Ness A, Dias T, Damus K, et al: Impact of the Recent Radomized Trials on the Use of Progesterone to Prevent Preterm Birth: A 2005 Follow-up Survey. *Am J Obstet Gynec* 2006; 195:1174.

[5] Green MF: Progesterone and Preterm Delivery – Déjà Vu All Over Again. *N Engl J Med* 2003; 348:2453.

terone, at least in early pregnancy, is widespread in the various artificial reproductive programs and is growing in its use as an agent to reduce prematurity.

Over the years, there has been an extraordinary amount of confusion related to the use of progesterone support in pregnancy. The Food & Drug Administration (FDA) created some of this confusion. In various labeling of progesterone products by the FDA, one of the contraindications to the use of oral progesterone is listed as "known or suspected pregnancy."[6] And, yet, no such contraindication is identified for the use of progesterone gel. In fact, progesterone gel is indicated for progesterone supplementation or replacement as a part of an assisted reproductive technology (ART) treatment program for infertile women with a progesterone deficiency.[7] To make this even more confusing, oral progesterone, while it was contraindicated in "known or suspected pregnancy," its official labeling stated that it "should be used during pregnancy only if indicated (see contraindications)." Also, up until very recently, there was a dire "warning" contained in the labeling for USP progesterone injection in sesame seed oil regarding an increased possibility of birth defects.[8] An analysis of the fetal safety of isomolecular progesterone (Pregn-4-ene-3,20-dione) administration during the course of 1,310 pregnancies over a 35-year period of time (1979-2014) was undertaken to address this confusion.

Methods

All of the patients who were involved in this study were patients of the Pope Paul VI Institute for the Study of Human Reproduction. This is a Catholic program for the evaluation and treatment of reproductive disorders. There were 2,732 pregnant patients who made up the initial study population. Of these, 2,094 received progesterone during the course of their pregnancy and 638 did not. However, 667 of those pregnancies were cared for in other geographic locations by physicians not associated with the Institute and it was thought that followup with those patients was not adequate to utilize as part of this study. This left 2,065 patients who were cared for by the authors or other physicians at the Pope Paul VI Institute. Of these, 1,763 were 20.0 weeks of gestation or greater at the time of delivery. In that group, 1,310 pregnancies were supported by progesterone and 453 were not. This obstetrical practice has been a generally high-risk reproductive medicine/infertility population and made up the study and comparison group for this analysis.

The mean level of progesterone during the course of pregnancy on an every 2-week basis from 4 to 40 weeks gestation was identified along with 1 standard deviation away from the mean. The different segments of the curve were then divided into Zones 1,2,3 and 4. The indications for progesterone monitoring and supplementation included the following: the previous occurrence of one of the following – spontaneous abortion; infertility; stillbirth; prematurity (<37 weeks gestation); premature rupture of membranes

[6] Physicians Desk Reference (PDR), 57th Edition, Thomson PDR, Montvale, NJ 2003 pp. 3166.

[7] Physicians Desk Reference (PDR), 57th Edition, Thomson PDR, Montvale, NJ 2003 pp. 3121.

[8] Progesterone Injection, USP in sesame oil. Watson Pharma Inc., Product Literature, Morristown, NJ 2001.

(<37 weeks gestation); pregnancy-induced hypertension; or abruption of the placenta. A congenital uterine anomaly, a patient who received a cervical cerclage and/or patients who simply had a low progesterone during the early course of their pregnancy were also considered candidates for progesterone supplementation.

During the course of these pregnancies, progesterone was administered using progesterone in sesame seed oil either 100 mg or 200 mg intramuscularly every 3-4 days during the course of the pregnancy, and the maternal serum progesterone level was monitored every two weeks. The first progesterone level was drawn usually 16-18 days after the estimated time of conception. Conception was estimated using the Peak Day observation of the **CREIGHTON MODEL FertilityCare™ System** which was charted by most of these patients in this study. This day has been shown to be closely associated with the time of ovulation (+/- 2 days in 95.4% of cycles[9]).

In cases where the patient was not using the **CREIGHTON MODEL System** the pregnancy was dated by the use of the ultrasound measurement of the crown rump length or gestational sac obtained generally between the 6th and 9th week of pregnancy. The progesterone levels were drawn every 2 weeks prior to an injection of progesterone –72 to 96 hours following the previous progesterone injection – at the expected *trough* of the exogenously administered progesterone. In the evaluation of the normal progesterone curve during the course of pregnancy, it was found that there was virtually no difference in the progesterone curve between a normal primigravid and a normal multigravid pregnancy (this is described in detail elsewhere[10]).

The first patient who received progesterone received it in 1979 and this study is a compilation of all of the pregnancies in patients who received progesterone and were delivered through the physicians at the Pope Paul VI Institute through 2014. Beginning in 1985, an extensive chart review was begun for each of the pregnancies. Each record was individually reviewed including the prenatal form, all documentation of the delivery, any notes in the chart at the time of delivery, at the postpartum examination or in the nursing notes were evaluated and recorded. All letters regarding the health of the newborn that were provided by the pediatrician or family physician were also reviewed. This recording took into account the following factors: the age of the patient, geographic home location, gravidity and parity, the number of previous spontaneous abortions and any other reproductive history that might be important. In addition, the gynecologic history, pregnancy number, fetal age at the first visit, estimated date of delivery, the pregnancy outcome, gestational age at outcome and birth date were also recorded. Additional items included whether the delivery was vaginal or Cesarean section, a single or a multiple pregnancy, whether the patient had a cerclage or not, whether she developed toxemia, had a previous induced abortion, previous infertility, a placenta previa and/or premature rupture of membranes. Furthermore, the development of fetal

[9] Hilgers TW, Abraham GE, Cavanagh D: Natural Family Planning – I. The Peak Symptom and Estimated Time of Ovulation, *Obstet Gynecol* 1978; 52:575.

[10] Hilgers TW: Assessing Progesterone during Pregnancy. In: Hilgers TW: The Medical and Surgical Practice of NaProTECHNOLOGY. *Pope Paul VI Institute Press* 2004, pp 713ff.

distress in labor was recorded, the presence of postpartum depression, chronic hypertension, adherent placenta, postpartum bleeding, placental abruption, the presence of fetal anomalies and what that anomaly was, the use of progesterone in the pregnancy, the use of terbutaline or any other tocolytic and IV antibiotic use were all recorded. In addition, in many of the pregnancies, the Apgar scores were also identified. This review of the record was then made on an every 2-year basis to compile the record for which this long-term study was accomplished.

In addition to that, there was a subgroup of 686 patients who were reviewed for the total amount of progesterone given to them during the course of their pregnancy and what the route of administration was (intramuscular, oral or vaginal). This was then recorded and evaluated. Some patients received intramuscular progesterone only (n=496, 72.3%) while others received only oral progesterone (n=10, 1.5%) or only vaginal progesterone (n=13, 1.9%). A combination of 2 or more of these routes of administration occurred in 167 patients for a total of 24.3%. At all times, isomolecular or bioidentical progesterone (Pregn-4-ene-3,20-dione) was used.

Results

The age, gravidity, parity, history of infertility and mean number of previous miscarriages was recorded for those patients who were on progesterone and compared to those who were not on progesterone. The patients who took progesterone were, on average, older (29.9 vs 26.3 years), had had more pregnancies (3.2 vs. 2.6), a more prominent history of infertility (45.2% vs. 12.7%) and the mean number of spontaneous abortions was larger in the group who had taken progesterone (0.8% vs. 0.3%). These were all in the highly significant range. Parity was basically the same between the 2 groups.

In a large subgroup of those patients (n=686) who received progesterone by the intramuscular route (n=661), the average total amount of progesterone they received during the entire course of the pregnancy, was 4,961.2 mg. For those who received oral progesterone (n=142), they received 37,245.8 mg of progesterone during the course of their pregnancy, and those who received vaginal progesterone (n=59) received a total of 67,769.5 mg (Table 2). The differences between the different groups are a representation of the different absorption capabilities of the different routes of administration with the absorption of progesterone through the intramuscular route being the highest and most rapid.

The various fetal anomalies that were observed, both in those patients who took progesterone (n=1,310) and those who did not take progesterone (n=453) is shown in Table 1. The total number of anomalies observed in those taking progesterone was 29 (in 1,310) for an incidences of 2.2%. The total number of anomalies observed in those who did not take progesterone was 10 (in 453) for an incidences also of 2.2%. By Chi-square analysis, this is not statistically significant (p=0.99). Looking at the individual anomalies, there was no statistically significant difference between those that were on progesterone and those that were not on progesterone for any of the anomalies identified.

Table 1

Specific Fetal Anomalies Observed in Patients On Progesterone (n = 1,310) vs. Those not on Progesterone (n = 453)

Pope Paul VI Institute for the Study of Human Reproduction (1979 – 2014)

Anomaly Observed	On Progesterone (n = 1,310) n	%	Not On Progesterone (n = 453) n	%	P Value
Down syndrome	5	0.4	0	0.0	0.19[1]
Cardiac anomaly	4	0.3	1	0.2	0.77[2]
Trisomy 13	3	0.2	1	0.2	0.97[3]
Cleft lip/palate	3	0.2	1	0.2	0.97[3]
Other chromosome Anomalies	2	0.2	1	0.2	0.76[4]
Polydactyly	2	0.2	0	0.0	0.41[5]
Renal anomalies	1	0.1	1	0.2	0.43[6]
Omphalocele / BW	1	0.1	1	0.2	0.43[6]
Imperforate anus/ club foot/ectopic anus	2	0.2	0	0.0	0.41[5]
Aqueductal stenosis	1	0.1	0	0.0	0.56[7]
Labial fusion	1	0.2[8]	0	0.0	0.57[8]
Hypospadias	1	0.2[9]	0	0.0	0.53[9]
Wilms tumor	1	0.1	0	0.0	0.56[7]
Rhabdomyoma of Heart	1	0.1	0	0.0	0.56[7]
Wiskott Aldrich Syndrome	1	0.1	0	0.0	0.56[7]
Dandy Walker Malformation	0	0.0	1	0.2	0.089[10]
Pyloric stenosis	0	0.0	1	0.2	0.089[10]
Tracheal atresia	0	0.0	1	0.2	0.089[10]
UPJ Obstruction	0	0.0	1	0.2	0.089[10]
Total	29	2.2	10	2.2	0.99[11]

1 = Chi-square analysis (Chi-square = 1.727,1)
2 = Chi-square analysis (Chi-square = 0.0848,1)
3 = Chi-square analysis (Chi-square = 0.0010,1)
4 = Chi-square analysis (Chi-square = 0.0915,1)
5 = Chi-square analysis (Chi-square = 0.6914,1)
6 = Chi-square analysis (Chi-Square = 0.6176,1)
7 = Chi-square analysis (Chi-square = 0.3458,1)
8 = Based upon 549 females exposed to progesterone and 218 not exposed, Chi-square analysis, (Chi-square = 0.3976,1)
9 = Based upon 570 males exposed to progesterone and 226 not exposed, Chi-square analysis (Chi-square = 0.3970,1)
10 = Chi-square analysis (Chi-square = 2.887,1)
11 = Chi-square analysis (Chi-square = 6.049e-005,1)

Many of the anomalies that were identified were chromosomal in nature and would have occurred at the time of conception and would not be associated with any drug taken after pregnancy occurred. There were more chromosomal anomalies in those who

took progesterone (n=14, 1.1%) than those who were not on progesterone (n=3, 0.7%). However, the difference is not statistically significant (p=0.45, Chi-square analysis). The number of non-chromosomal anomalies in those taking progesterone was lower (n=15, 1.1%) than those who were not on progesterone (n=7, 1.5%). These would be the anomalies that might be related to a teratogenic effect of a particular medication, but again, there was no statistically significant difference (p=0.51, Chi-square analysis).

The most frequent route of administration was intramuscular progesterone and it was often given in this particular population of patients into the 2nd and 3rd trimesters of pregnancy. This was because the serum progesterone levels in the mother were in Zone 1 or lower Zone 2 during the course of that pregnancy into the 2nd and 3rd trimesters.

Discussion

A number of approaches to the use of progesterone support in pregnancy have been utilized over the years. These support programs are noteworthy in their lack of uniformity. The two that have generally been used are 17 *a*-hydroxyprogesterone caproate (17 0HP-C) and progesterone (P). It has been an edict of contemporary reproductive medicine that progesterone should not be administered after the first trimester of pregnancy. However, in this day of "evidence-based medicine," there is little evidence upon which to base this edict since progesterone levels are generally not followed.

The corpus luteum is the major source of progesterone during the first 9-10 weeks of pregnancy. There is, however a shift in progesterone production from the corpus luteum to the placenta between the 6th to the 11th week of pregnancy. During the 2nd and 3rd trimesters of pregnancy, it has generally been thought that the placenta is the major source of progesterone production. However, it has also been shown that the corpora lutea of pregnancy continues to produce progesterone during this period of time.[11] Progesterone concentrations in the peripheral vein of women at term were the same as the progesterone concentration in the ovarian vein coming from the ovary where there was no corpus luteum. The progesterone concentrations from the ovary in which a corpus luteum was present, however, were more than twice that of the progesterone levels in the peripheral vein.

In women who have preterm labor, serum levels of progesterone and 17 *a*-hydroxyprogesterone are significantly decreased during the 2nd and 3rd trimesters of pregnancy. Progesterone has an inhibitory effect on uterine muscle contractility. The effect of progesterone on uterine contractility may be mediated through the inhibition of prostaglandin-induced myometrial activity which is inhibited by progesterone; and, progesterone may decrease the number of gap junction formations in the myometrium. Progesterone is also found in very large concentrations in the myometrium of the pregnant uterus and that concentration can be increased further with the oral administration of micronized isomolecular progesterone. The observation that there is an increased

[11] LeMaire WJ, Conly PW, Moffett A, Cleveland WW: Plasma and Progesterone Secretion by the Corpus Luteum of Term Pregnancy. *Am J Obstetrics Gynec* 1970; 108:132.

frequency of uterine contractions associated with an increased likelihood of preterm delivery is further evidence of the important association of these findings.

For over 35 years, the senior author has been supplementing pregnancies with progesterone. This project began with the use of progesterone in early pregnancy in patients with infertility or a previous history of miscarriage. The initial goal of progesterone therapy was to decrease the incidence of miscarriage in subsequent pregnancies.

As this project began to grow, it was difficult to determine the dosage of progesterone that should be given and an objective means by which the pregnancy could be monitored. This led to the measurement of serum progesterone levels during the course of pregnancy. Eventually, a standard curve for progesterone in pregnancy (a normogram) was developed and the ability to objectively assess progesterone became possible (this is explained in detail elsewhere).

The Pope Paul VI Institute Progesterone Support Program has several important features to it:

1. First and foremost, is its ability to objectively monitor the dose of progesterone being provided based upon the serial monitoring of serum progesterone levels during pregnancy.
2. Its selection of progesterone over the use of 17 *a*-hydroxyprogesterone caproate (17-0HP-C).
3. Its use during the course of pregnancy where supplementation can be objectively quantified. Thus, it is not limited to the use in only the first trimester of pregnancy but often extends into the 2nd and 3rd trimesters.
4. Its proven safety.

Progesterone has been selected as the hormone of choice for the support of pregnancy over and above 17 *a*-hydroxyprogesterone caproate (17-0HP-C). 17 *a*-hydroxyprogesterone hexonate (17-0HP-H) or medroxyprogesterone acetate (MPA). The selection of isomolecular progesterone was based upon the following factors:

1. Isomolecular progesterone (Pregn-4-ene-3,20-dione) is the main natural support hormone of pregnancy.
2. 17-0HP-C, 17-0HP-H and MPA are all synthetic analogs of 17-alpha hydroxyprogesterone and progesterone and are thus chemically different from natural progesterone. This likely decreases their ability to bind to myometrial progesterone receptors.
3. 17-0HP-C, which is most commonly used and the subject of one of the recent revival papers, was manufactured under the trade name Delalutin (Bristol-Myers-Squibb Company), but its manufacture was discontinued in 1986 due to declining sales. It has been available through compounding pharmacies and, most recently, has once again appeared commercially but it is extraordinarily expensive in its commerical form.
4. While 17-0HP-C can be considered safe in pregnancy (as is progesterone), MPA has still a few lingering questions remaining with regard to safety.

5. Progesterone is a completely natural hormone. That is, it is a hormone manufactured in abundance by the human body during pregnancy while the others are all foreign to the body and not manufactured by it.

The key to the objective supplementation of progesterone during pregnancy is the availability of a meaningful standard curve (or normogram) for the production of progesterone during the course of pregnancy. These curves are not available in most laboratories. The National Women's Hormone Laboratory of the Pope Paul VI Institute, however, has developed such a curve in the many years of its work in the use of progesterone-supported pregnancy. The standard curves for normal pregnancy have been worked out using radioimmunoassay procedures and chemiluminescence technology.

During the course of pregnancy, progesterone levels are drawn on an every 2-week basis, and progesterone is supplemented based upon the progesterone level. The dosage of progesterone administered is determined based upon the zone that the progesterone level is in.[10] When the progesterone level is drawn, it is always drawn immediately prior to the administration of the subsequent progesterone dose. In this way, the progesterone level is drawn at the bottom of the natural absorption pattern of the exogenously administered progesterone and is thus drawn at its trough. In this way, a best estimate of the baseline production of progesterone during the course of that pregnancy can be obtained and an objective decision can be made relative to the next dosage of progesterone to be administered. The goal of treatment is to see that the serum progesterone level during pregnancy reaches either the mean level or is in Zone 3 or Zone 4.

Green has pointed out that the problems identified with the use of diethylstilbestrol (DES) has cast "a long shadow" on the use of hormonal supplementation in pregnancy.[5] In addition, there appears to be an extraordinary amount of confusion related to the use of progesterone support in pregnancy. Furthermore, the Food & Drug Administration (FDA), which is quite capable of relieving this confusion, has instead continued the confusing story and some of this needs to be addressed.

Much of the confusion surrounds a user-unfriendly nomenclature as it specifically relates to progestational agents. The term "progesterone" is often used loosely to refer to any progestional agent including both C21 and C19 agents. But progesterone is progesterone and nothing more. It is produced naturally in the human body along with other naturally-occurring progestational agents such as 20 alpha-dihydroprogesterone, 20 beta dihydroprogesterone, and 17 *a*-hydroxyprogesterone. Progesterone is the only known natural progestational agent with major biologic signficance and 17 *a*-hydroxyprogesterone is virtually inert. A new nomenclature has been suggested in an attempt to clarify these difficulties. Those progestational agents which are natural to the human body, i.e., are actually manufactured physiologically within the body, are best referred to as isomolecular hormones (IMH) and by their specific name. Those pregestational agents which are artificial to the body, i.e., are not manufactured physiologically in the body, are best referred to as heteromolecular artimones (artificial substitutes for naturally-occurring hormones). In this way, one can begin to distinguish between those

compounds which are naturally occurring to the body and which are foreign to it. This becomes important as one looks at the overall question of safety. IMH progesterone is a C21 steroid deriving from the pregnane nucleus. There are certain HMA artimones that are also C21 compounds. These include 17 *a*-hydroxyprogesterone caproate (17-0HP-C) and medroxyprogesterone acetate (MPA).

There are also C19 steroids derived from the androstane nucleus. Testosterone is the prototypical C19 steroid. While testosterone is a naturally-occurring C19 steroid with obvious androgenic properties, there are a number of artificially-derived C19 compounds which are less androgenic, but also have progestational activity. These include compounds such as norethindrone (19-norethinyltestosterone), norethynodrel, norgestrel, and ethisterone (ethinyl testosterone). These 19-nortestosterone derivatives unequivocally can masculinize the female fetus if given in high doses at susceptible times of embryogenesis.

The effect of these 19-norcompounds was recognized by Wilkins and Jones, et al, in 1958 and this study continues to be cited as a cause for confusion. This study, from Johns Hopkins University, presented 21 cases of females that showed evidence of masculinization of the external genitalia. In 12 of these cases, there was *in utero* exposure primarily to the C19 artimone, ethisterone (ethinyl testosterone). In 3 cases, no steroids were used in pregnancy and in the remaining 6 cases, IMH progesterone was used. However, of those 6 cases, 3 were also exposed to ethisterone and one to methyltestosterone, explaining the defect. In the other cases, the women also received stilbestrol. There is evidence that this can also exert a masculinizing influence.

In an extensive review of the fetal effects of progestational agents (both natural and artificial), Simpson and Kaufman concluded that despite many cohort and case-controlled studies, there still remains little reason to suspect that progesterone exposure *in utero* exerts a deleterious effect on fetal development. The exceptions are the 19-nortestosterone derivatives, which in high does (10-20 mg daily) can cause genital virulization.[12] They concluded that the evidence is considerable that progesterone does not cause a general increase in birth defects, are not cardiac teratogens, do not cause limb reduction defects, do not cause neural tube defects or hydrocephalus and the frequency of esophageal atresia has not been increased in any of the studies and *in utero* exposure is unlikely to result in abnormal development of the male genitalia. Other reviews have come to similar conclusions.

With the experience presented in this report, the incidence of fetal anomalies in patients on progesterone was 2.2% versus those who were not taking progesterone (2.2%). The difference is not statistically significant (p=0.99 - Chi square analysis). We observed one male infant with hypospadias with an incidence of less than 0.1%. This is significantly lower than the quoted incidence of 5-8/1,000 (0.5-0.8%), and even more signficantly different than the claim that progesterone may be associated with doubling of

[12] Simpson JL, Kaufman RH: Fetal Effects of Estrogens, Progestogens and Diethylstilbestrol. In: Fraser IS, Jansen RPS, Lobo RA, Whitehead MI: Estrogens and Progestogens in Clinical Practice. *Churchill Livingstone, London* 1998, pp. 533-553.

that frequency. It was also observed that one female infant had mild labial fusion treated effectively with estrogen cream (incidence of 0.1%). But this, too, is much lower than the reported incidence of 1.8%. In both cases, there was no significant difference in the incidence between those on progesterone versus those who did not take progesterone.

This series of patients is the largest database on the use of progesterone that has ever been reported for isomolecular (bioidentical) progesterone supplementation in pregnancy. Furthermore, nearly all of these patients had exposure to progesterone during the first 4 months of pregnancy and no increase in any of the anomalies was observed.

It was observed that the incidence of Down syndrome was more common in the group that received progesterone than those that did not (however, it was not a statistically significant increase). Because the number of patients in the progesterone group who had a previous history of infertility and more previous spontaneous abortions, it is suggested that this increased incidence might be related to that previous history. In both cases, the number of anomalies in the progesterone versus the non-progesterone group, whether they were chromosomal or non-chromosomal was not significantly different from those that were not on progesterone.

In conclusion, specifically as it relates to the naturally occurring hormone progesterone (Pregn-4-ene-3,20-dione), there is no credible evidence to suggest that if it is used to support pregnancy, that it is teratogenic or responsible for genital malformations. This is true whether that support is in the early days of pregnancy or later in pregnancy.

The Reversal of Mifepristone With Progesterone

George Delgado, M.D., FAAFP

Actions of Progesterone

Progesterone has the following physiological actions:

- Prepares the endometrium for implantation of the embryo.
- Promotes decidua development (placental component).
- Inhibits myometrial contractions.
- Promotes growth of breast milk producing cells.
- Inhibits milk production.

Pharmacological blockage of progesterone receptors, of course, inhibits all of these actions. The class of drugs capable of blocking progesterone receptors is known as selective progesterone receptor modulators (SPRM) includes mifepristone, AKA RU-486. Mifepristone (Mifeprex) has been available in US since 2000. By 2008 1/4 US abortions prior to 9 weeks were accomplished with mifepristone (about 200,000/year). 18% of abortions are performed with mifepristone. More than 2 million unborn children have been killed by mifepristone and misoprostol. Mifepristone is followed two days later by a second drug, misoprostol, to complete the abortion. Some clinics are using mifepristone off label up to 63 days after LMP.

FDA Approved Protocol

FDA approved the combination of mifepristone and misoprostol for induced abortion up to 49 days after LMP:

- Day 1: mifepristone (Mifeprex) 600 mg po
- Day 3: misoprostol (Cytotec) 400 mcg po
- Day 14: confirmation of embryo demise

Off-Label Protocols Used up to 63 days after LMP (and later)

- Day 1: mifepristone (Mifeprex) 200 mg po
- Misoprostol (Cytotec) 800 mcg per vagina 6-72 hours after mifepristone.

Or

- Misoprostol (Cytotec) 800 mcg per buccal mucosa 24-36 hours after mifepristone

Efficacy FDA Trials of Mifepristone + Misoprostol

The rates of incomplete abortion were 5% before 49 days and 7-8% at 50-63 days. ("Incomplete abortion" means the uterus did not completely empty.) The rates of surviving embryo were <1% before 49 days and 9% if given at 57-63 days. [Spitz IM et al. "Early pregnancy termination with mifepristone and misoprostol. NEJM 338:18 (April 30,1998)1241-47.]

Efficacy Mifepristone Only: 60-80% Completed Abortion Rate

Embryo survival rate unknown. [Kovacet et al 1984, Couzinet et al 1986 both sited page 553 Induced Abortion Chapter 3, Obstetrics and Gynecology for Postgraduates volume 3, 3rd edition]

Mifepristone Physiology and Pharmacology

Mifepristone was first studied for its anti-glucorcorticoid properties. Mifepristone binds glucocorticoid receptors four times as avidly as dexamethasone. Thus mifepristone was investigated for use in Cushing syndrome. Mifepristone has also been studied as a treatment for endometriosis and uterine fibroids. Mifepristone also inhibits ovulation, and prevents implantation, and is thus also used in some areas of the world as a contraceptive.

Mifepristone Pharmacology

Mifepristone has a 70% oral absorption. After first-pass, 40% is bioavailable. Mifepristone binds to progesterone receptors twice as well as progesterone. It also binds to serum transport protein alpha 1-acid glycoprotein.

Demethylation and hydroxylation is catalyzed by CYP3A4. Three metabolites retain biologic activity. Serum half-life is 18-25 hours versus progesterone 25-55 hours. Metabolites can be measured up to 72 hours after a dose.

Abortion Pill Reversal

Statistics May 2012 to November 2014

- Total calls: 622
- Patients that received progesterone minus those who later took misoprostol or had a surgical abortion: 248 (40% of patients that called received progesterone)
- Success with progesterone protocol: 149 (65 births, 84 currently pregnant) 60% of patients that received progesterone are pregnant or have delivered a healthy baby
- Loss of pregnancy despite receiving progesterone: 97

Abortion Pill Reversal Assists United States

International Clients

Text Message From a Satisfied Patient:

> Hello Liz!!! I just got home. Yes I got the shot and I am going to return tomorrow also!!! I just wanted to say thank you from the bottom of my heart!!! You really saved me!!! I knew I had done wrong!! It was by chance I got your number and I am so glad I did!!!! I feel relieved!!!! You are my saving grace!!! God bless you Liz!!!

Birth Defects Associated with Misoprostol

- Moebius Syndrome
- Unilateral or bilateral palsy of the abducens (VI) and facial (VII) cranial nerves.
- Other cranial nerves
- Craniofacial or orofacial anomalies
- Limb malformations are often associated.

Etiology remains largely unknown and probably involves multiple factors. The critical period formal formation appears to be 5-8 weeks of gestation.

Mifepristone and Birth Defects

To date, mifepristone alone does not appear to have induced Möbius syndrome. Bos-Thompson MA, Hillaire-Buys D, Roux C, Faillie JL, Amram D., *Ann Pharmacother*. 2008 Jun;42(6):888-92. doi: 10.1345/aph.1K550. Epub 2008 May 6. Drugs in Pregnancy and Lactation: Mifepristone:

- Teratogenic in rabbits
- No teratogenesis in monkeys and rats
- Human data insufficient

Gerald G. Briggs, Roger K. Freeman, Sumner J. Yaffe -2011
The American College of Obstetricians and Gynecologists released a Practice Bulletin in 2014 stating that mifepristone is not assoicated with birth defects.

Studies on Malformation Rate After Mifepristone Exposure

1) BJOG. 2013 Apr;120(5):568-74. doi: 10.1111/1471-0528.12147. Epub 2013 Jan 24. *Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study.* Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. http://www.ncbi.nlm.nih.gov/pubmed/23346916 A total of 105 pregnancies were included, with 46 exposed to mifepristone alone, and 59 exposed to both mifepristone and misoprostol. There were 94 live births (90.4%) and 10 (9.6%) miscarriages (including one with major malformation). Elective termination of pregnancy was performed after the subsequent diagnosis of trisomy 21 in one case. The overall rate of major congenital malformations was 4.2% (95% CI 1.2-10.4%), with two cases among 38 patients exposed to mifepristone alone, and two cases among 57 patients exposed to both mifepristone and misoprostol.
CONCLUSIONS:
This first prospective study found that the rate of major malformations after first-trimester exposure to mifepristone is only slightly higher than the expected 2-3% rate in the general population. Such findings provide reassuring data for risk evaluation for continuation of pregnancy after mifepristone exposure.

Studies on Malformation Rate After Misoprostol Exposure

1) http://www.ncbi.nlm.nih.gov/pubmed/23207166 *Reprod Toxicol*. 2013 Apr;36:98-103. doi:10.1016/j.reprotox.2012.11.009. Epub 2012 Dec 1. *Birth*

defects after exposure to misoprostol in the first trimester of pregnancy: prospective follow-up study. Vauzelle C, Beghin D, Cournot MP, Elefant E.

Misoprostol during the first trimester of pregnancy is associated with a specific malformative pattern (Moebius sequence and limb defects) whose incidence remains unknown. Data originate mostly from illegal use for abortion and are mainly retrospective. The present prospective controlled study analyses outcomes of first trimester misoprostol exposures after medical prescriptions. Malformation rate was higher among 236 pregnancies exposed before 12 gestational weeks (4%) than in 255 controls (1.8%), although not statistically significant (OR=2.2 [95% CI=0.6-7.7]). Three malformations (2%) in the exposed group were consistent with the misoprostol malformative pattern. This is the largest prospective study on first trimester misoprostol exposure and the first one relying on prescriptions. A trend toward a doubling of the overall rate of malformations was observed and for the first time an estimation of the incidence of misoprostol specific spectrum is proposed (2%). Brainstem injuries including severe trismus might be added to this specific pattern.

2) *Arch Argent Pediatr*. 2011 Jun;109(3):226-31. doi: 10.1590/S0325-00752011000300007. [*Misoprostolteratogenicity: a prospective study in Argentina*]. [Article in Spanish] Barbero P, Liascovich R, Valdez R, Moresco A.

RESULTS: Among women exposed to misoprostol only the 8.2% purchased it on prescription, 81.5% heard about its abortifacient effect by friends, neighbors or relatives, the average dose was 1.439 µg which was used both orally and vaginally by the 77.2%; the mean gestational age was 48.5 days and 35.2% used an additional abortive agent. Women exposed to misoprostol had a significantly higher frequency of abortions (exposed: 17/94= 18.1%, unexposed, 29/401= 7.2%, RR= 2.27, 95%: 1,30-3,98), and offspring with major congenital abnormalities (exposed: 5/77= 6.49%, unexposed: 8/372= 2.15%, RR= 3.02, 95%:1,02-8.98).The five malformed children prenatally exposed to misoprostol showed: 1) encephalocele and transverse limb defects; 2) porencephaly, 3) pulmonary adenomatous cystic malformation, 4) occipital encephalocele and, 5) intestinal malrotation.

CONCLUSIONS: The study found a significant association between prenatal exposure to misoprostol and the occurrence of major congenital anomalies.

3) *Reprod Toxicol*. 2006 Nov;22(4):666-71. Epub 2006 Jun 5. Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. da Silva Dal Pizzol T, Knop FP, MengueSS.

Abstract: The present systematic review was proposed with the objective of estimating the risk of congenital anomalies and other adverse events in children exposed to misoprostol during fetal life. The data source consisted of case-control studies that analyzed the effect of prenatal exposure to misoprostol on the pregnancy outcome, which were located in electronic databases and published up to June 2005. The outcomes of interest included congenital anomalies, fetal death, low birth weight and prematurity. The odds ratios (OR) for the individual studies were pooled by meta-analysis. Sensitivity

tests and heterogeneity analysis were performed. Four studies involving 4899 cases of congenital anomalies and 5742 controls were included in accordance with the selection criteria. None of the studies analyzed other adverse effects from misoprostol on the outcome from gestation. Increased risks of congenital anomalies related to misoprostol use were found for any congenital defect (OR=3.56; 95% CI: 0.98-12.98), Möbius sequence (OR=25.31; 95% CI: 11.11-57.66) and terminal transverse limb defects (OR=11.86; 95% CI: 4.86-28.90). In conclusion, prenatal exposure to misoprostol is associated with an increased risk of Möbius sequence and terminal transverse limb defects.

Progesterone Safety

- An article looked at babies with hypospadias compared to those without. The mothers of those with hypospadias were more likely to have taken a progestin (no distinction was made as to which type). Arch Pediatr Adolesc Med. 2005 Oct;159(10):957-62.
- A 1999 FDA review concluded that there is no risk of birth defects, including hypospadias, in pregnant women taking progesterone or 17-hyroxyprogesterone.
- The rate of hypospadias in Dr. Hilgers' group who took progesterone was 1 in 1000 while the rate in the general population is actually higher at 1 in 250. Hilgers TW, The Medical and Surgical Practice of NaProTECHNOLOGY, Pope Paul VI Institute Press, Omaha, NE 2004, pg740

Statement from The American Society of Reproductive Medicine

While long-term adverse consequences of progesterone therapy have not been identified in humans and appear unlikely, the safety of this or any drug cannot be absolutely guaranteed. The FDA requires inclusion of a package insert regarding synthetic progestins with each progesterone prescription. These drugs have some progestational effects but also have other effects which progesterone does not have, including male hormone effects. Synthetic progestins may not be safe in pregnancy. American Society of Reproductive Medicine https://www.asrm.org/detail.aspx?id=1881.

Challenges and Barriers to Abortion Pill Reversal:

- Concerns regarding possible birth defects
- Ambivalence and indecision
- Difficulty tracking patients
- Lack of emotional support
- Abortion clinic pressures
- Lack of bonding with unborn baby
- Working against the clock to find a doctor
- Lack of progesterone at offices

Ambivalence and Indecision

The patients have mixed feelings about continuing the pregnancy. Some have taken misoprostol, even after starting progesterone. The influence of family and friends can be positive or negative. The discomfort of progesterone injections can be a deterrent to continuing.

Difficulty Tracking Patients

Many medical abortion patients are young and immature. Many do not answer calls or return text messages while they discern what to do. They can just seem to disappear. Some reappear just as abruptly. Getting data from physicians can be difficult.

Lack of Emotional Support

Some patient have families who want them to abort, and exert considerable and continuous pressure. Some may be kicked out of their homes. Boyfriends often abandon them or are already absent when the pregnancy is discovered. Many lack financial resources.

Abortion Clinic Pressures

A recent patient thought she was just going for a consultation; before she knew it, she was given a pill and a glass of water. Numerous patients have been told they have to "finish what you have started." They have been told there is no chance of reversal. Birth defect risks have been exaggerated. One compared the situation to "shooting your dog and watching it die slowly."

Lack of Bonding With the Unborn Baby

Abortion clinic usually will only tell them pregnancy is intrauterine and the gestational age. Often, family members are not allowed into ultrasound room with them. Patients often do not look at ultrasound monitor and are not encouraged to do so.

Finding a Doctor

If the patient is in an area where we do not have a doctor, it can be very time-intensive finding one. Office staffs sometimes do not know that the doctor is in the APR network. Sometimes doctors in our network are not prepared when we need them. Pitfalls are often experienced with novel situations and protocols.

Lack of Progesterone in the Office

Offices that do not routinely use injectable progesterone may not always have it or forget to order it. They must keep an eye on the expiration date and reorder as needed. Shelf life of compounded progesterone ranges from 3 to 6 months.

Considering a Potential Protocol

Our growing case series suggests that the effects of mifepristone can be stopped by the administration of progesterone. Our goal is to have the progesterone out-compete the mifepristone at the progesterone receptor. There is no scientific evidence suggest-

ing that mifepristone significantly increases the risk of birth defects. Progesterone and 17-hydroxyprogesterone caproate are safe in pregnancy.

The molecular weight of progesterone is 314.7 while that of mifepristone is 429.6. The half-life of progesterone is 25-55.3 hours. The half-life of mifepristone is about 18-25 hours. Mifepristone and its metabolites can be measured up to 72 hours after an ingested dose. Mifepristone binds to the receptor about twice as avidly as progesterone. It would seem that if we could dose the antidote at twice that of the poison, or as close as possible, we would have the best chance of success since mifepristone binds twice as avidly to the receptor and the molecular weights are similar. We suggest the highest, most bioavailable dose, progesterone in oil 200 mg IM.

The Protocol

- Give progesterone 200 mg intramuscular (IM) as soon as possible after ingestion of mifepristone.
- Perform transvaginal or transabdominal ultrasound as soon as possible to confirm embryonic or fetal viability. Do not delay the administration of progesterone if ultrasonography is not available immediately.
- If less than 6.5 weeks after LMP, you may monitor serial HCG levels. Interpret the results carefully.
- Repeat progesterone 200 mg IM q day for two more days then every other day until day 14 after the ingestion of mifepristone.
- Then, treat with progesterone 200 mg IM twice a week until the end of the first trimester.

Potential Difficulties With The Protocol

- Some women refuse intramuscular progesterone.
- Some physicians do not have progesterone in oil for injection.
- 17-hydroxyprogesterone is very expensive.
- Medroxyprogesterone acetate (Provera) is associated with birth defects.

Alternate Protocols

- Progesterone compounded vaginal suppositories 400 mg self-administered each night until the end of the first trimester
- Progesterone (Prometrium) 200 mg oral capsules 2 capsules self-administered vaginally each night until the end of the first trimester
- Progesterone (Prometrium) 200 mg oral capsules 2 capsules orally each night (or twice a day) until the end of the first trimester

Some clinicians monitor progesterone levels after the first trimester, and administer progesterone if the levels are low. See Hilgers TM The Medical and Surgical Practice of NaProTECHNOLOGY 2006, The Pope Paul VI Institute for the Study of Human Reproduction or www.naprotechnology.com.

Prepare for the Protocol

- Have progesterone in oil on hand, 100 mg/ml compounded to minimize injection volume.
- Off the Shelf 50 mg/ml
- Maintain a list of Compounding Pharmacies. Find one you trust nationally or in your area.

Compounding Pharmacies

- International Academy of Compounding Pharmacists www.iacprx.org 800-927-4227
- Kubat Pharmacy Inc. 402-558-8888 www.kubatpharmacy.com
- Central Coast Pharmacy Specialists 800-238-5999

Proper Technique

- Inject high and lateral. (Upper outer quadrant, gluteal)
- *Warm to body temperature.
- *Use a 25 gauge 1 ½ inch.
- *Inject slowly, by the clock.

Be Available

- abortionpillreversal.com
- More Than 200 APR Doctors
- Get Doctors, NPs, Midwives or PAs to Join
- Contact pro-life medical professionals in your area and invite them to be part of our APR network.

Our Goal: US saturation, and worldwide saturation.

Calling All Pregnancy Resource Centers

- With a medical director, can be in the APR network.
- Can serve as the hub.
- Provide needed counseling and support.
- Keep progesterone in the office.
- RN can administer injections with a physician order.
- Make phone calls and follow patients.

Resources for PRC Hubs and Doctors

- 24/7 hotline is staffed by nurses.
- Consent forms
- Supportive follow-up, as needed
- Model standing orders
- Model policies and procedures
- Protocol
- Advice available from nurses and Dr. Delgado

Four-Prong Approach for Recruitment

- Obstetrician gynecologists
- Primary Care Providers
- Pregnancy Resource Centers
- Education

Keep the Hope Going!

- www.abortionpillreversal.com
- DONATE!
- JOIN!

To find out more about our network send an email or make a call to:

- Sara Littlefield or Debbie Bradel, RN apreversal@gmail.com USA 619-577-0997
- George Delgado, M.D. at gdelgadomd@yahoo.com or
- Erica Tobin at USA 760-715-6010 etobin@colfs.org

Practicing Medicine with Integrity in a Hostile Culture

Bogdan Chazan, M.D., Ph.D.*

In the middle of last year, Poland witnessed a case related to obstetrics care, abortion and physicians' conscience clause. The case illustrates a struggle between the civilization of life and the civilization of death. I was involved in it and would like to present the background and the course of those events, as well as provide a wider commentary and conclusions.

I am a doctor, a specialist in gynecology and obstetrics. Twelve years ago, I was dismissed from the position of National Consultant in the Field of Obstetrics and Gynecology in Poland and from the position of head of the clinical department of obstetrics and gynecology at the Institute of Mother and Child for defending the life of an unborn child. As National Consultant, I expressed the opinion that Down's syndrome does not meet the criteria of a severe disease threatening the fetus's life, which would justify performing an abortion. Feminist organizations filed a complaint with the Public Prosecutor's Office, accusing me of disrespecting women's "reproductive rights." After the hearing, the Public Prosecutor's Office dismissed the case, but I was removed from clinical practice.

I found employment as an administrator, director of the municipal specialist Holy Family Hospital in Warsaw, which I combined with my work in the hospital as a consultant and with academic work at the university. I employed new, well-educated and experienced personnel; the hospital was completely modernized and expanded. In a year's time, it was going to be transformed into a Family Health Center. The high standard of medical care in the hospital attracted patients. The number of deliveries tripled, to 4,500 per year, and the perinatal mortality rate lowered to 4 per mille. In the hospital we did not perform abortions or in vitro fertilization (IVF), which the patients accepted. We were successful at obtaining funds from the European Union, as well as received prizes and awards.

In early spring last year Dr. Wanda Półtawska addressed physicians with an appeal to sign a "Declaration of Faith." The Declaration, the text of which was engraved on stone tablets, was placed by a delegation of Polish doctors at the feet of the icon of the Black Madonna of Częstochowa. For many years, Dr. Półtawska had cooperated with St. John Paul II; the Pope took her opinion into consideration when writing his

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encyclical "Evangelium Vitae." When signing that Declaration as one of more than 3,500 physicians, midwives, and medical students, I did not expect that it would raise any considerable confusion.

However, attempts were made in the media to discredit the Declaration signatories. Because of what happened in the past, it was me who was attacked most often. It was argued, for example, that having declared respect for the sanctity of the human body, I will no longer perform Caesarean sections. The Undersecretary of State in the Ministry of Health suggested that doctors who signed the Declaration will now treat the sick with holy water and called for using the encyclical at home, but rather an encyclopedia at work. The liberal media would like to see me, as a "Catholic-Taliban," in Afghanistan. Left-wing members of Parliament postulated that the doctors who signed the Declaration of Faith not be allowed to specialize in obstetrics and gynecology. A representative of the Boards of Physicians suggested that medical students who signed the Declaration of Faith should be dismissed from medical universities. These are examples of how severely and ruthlessly those who want to be faithful to natural law and their conscience are now treated in my country. The accusation that declaring one's faith can pose a risk to a patient's life or health is absurd. In fact, the opposite is true: a believing doctor who observes the commandment of love for their neighbor serves their patients well.

In April last year I refused in writing to perform an abortion at the Holy Family Hospital. The mother had experienced many obstetric failures in the past. The child was diagnosed with developmental defects within the skull. The referral center to which we sent the patient from our hospital for a consultation suspected hydrocephalus. A professor of pediatric surgery offered to provide care for the child after it was born, claiming that surgical correction of the developmental defects after the childbirth could not be excluded.

After a long conversation, instead of an abortion, I offered the mother care during the pregnancy and birth in our hospital, as well as psychological assistance at a perinatal hospice. However, the patient did not give up her plans to get an abortion. The Polish provisions concerning the conscience clause stipulate that a doctor or a midwife who, due to their conflict of conscience, cannot participate in performing a procedure is obliged to refer the patient to another doctor or another midwife who will perform it. It is a very strange and impractical provision. A person who wants to exercise the right to the conscience clause is obliged to help in the performance of such acts by other persons – thus, he or she has to indirectly participate in them. As a doctor and director, I did not want to and could not fulfill this obligation. In Poland, there is no list of doctors who perform abortions and have no moral objections. I would have had to phone doctors one by one, possibly risking an allegation of obtrusiveness. Imposing such an obligation proves inadequate protection of a doctor's conscience in Poland. It is contradictory to the principle of freedom of conscience. A complaint concerning the defectively constructed legal provision regarding the conscience clause has been filed by the self-government of physicians with the Constitutional Tribunal.

The child was born in another hospital, by Caesarean section, with head defects more serious than had been expected (anencephaly). One professor described his appearance in detail on television and called him a "monster" or "Chazan's child." The baby died within a couple of weeks.

A few weeks after I refused to perform the abortion, the patient filed a complaint with the City Hall in Warsaw, which is the founding institution of the Holy Family Hospital. Immediately after, five simultaneous inspections were ordered and carried out in the hospital by various institutions, including the Patient's Rights Office, the Screener for Professional Liability of the Supreme Board of Physicians and from the Public Prosecutor's Office. Such a number of inspections performed simultaneously is contradictory to the law. The National Health Fund fined the hospital with an equivalent of about 30,000 dollars. Boards of Physicians are threatening me with revoking my license to practice my profession. The patient is demanding about 300,000 dollars from the hospital for the suffering inflicted and is threatening me with a civil lawsuit. The Public Prosecutor's Office's investigation of my case is underway. One left-wing activist announced that I will certainly go to prison.

The case was highly publicized in the media, where it became a leading topic. I was ruthlessly attacked by left-wing and liberal politicians and journalists. The media published articles with false information and malicious comments. In response to that, the conservative media began to defend me. Statements emphasizing the necessity to defend human life were published by the Polish Episcopate and, independently from that, by many bishops. One of the commentators (Marian Machinek) wrote that "Doctor Chazan's attitude has become a symbol of practicing medicine that falls outside political correctness. For supporters of the cultural revolution such an attitude has become extremely dangerous. It gives support to the indecisive, who have always wanted to behave in a similar way, but lacked courage. It is also becoming a matter of conscience for those who surrendered and gave in to the pressure of the "applicable standards". Attitudes that are clear and accurate can tear down the sterile uniformity of the system." Supportive people, patients and their families organized a rally of support for me in front of the hospital, with a few hundred participants, and a Club of Hospital Friends was created. Some professors of law interpreted my point of view as a justified civil protest. A community fundraising event was also started in order to compensate the hospital for the fine imposed by the National Health Fund. The media abroad also became interested in this problem.

In this atmosphere of hot social debate, the Mayor of Warsaw and vice-president of the ruling party (Civic Platform)—Hanna Gronkiewicz–Waltz, commonly regarded as Catholic—dismissed me from my position. Earlier, she had not responded to my letter with a request for a conversation. She did not have the courage to personally hand me the document of dismissal, nor did she find the time to talk and to listen to any explanations. Later, in the media, she said that she shares my system of values, but she had to fulfill the requirements of the law. However, no provision of law stipulates

that for such a "crime" the maximum sentence—a dismissal from work—should be imposed, especially that the work duties were fulfilled in an exemplary way up to then. One commentator described this punishment as ethically unacceptable, unjustified, out of proportion, unjust and legally dubious.

The day after my dismissal from the position of the hospital director, a woman—pregnant mother—came with a referral for an abortion due to the child's illness. She was accompanied by television cameras. In the hospital, where no abortion had been performed for eight years, an atmosphere of intimidating the personnel, fear and crying set in. The midwives were told that it was a "disciplinary requirement," "a woman's decision," "an employee's duty." The abortion did take place. After I was dismissed, emotions grew even more intense. Some people accused me of disobeying the law, causing the suffering of the mother, who had to accompany her dying child, and causing the child's suffering. In their opinion, abortion could have shortened that suffering. A threat to my personal safety also appeared.

At the same time, many people expressed their support for my decision to refuse to perform an abortion and showed their compassion for my situation after I was dismissed from work. I received tens of thousands of letters and postcards, almost 200,000 declarations of support on the Internet from Poland and abroad through Citizen Go. According to these people, who I agree with, the life and human dignity of an ill child are even more worthy of protection than those of a healthy child. A disease, suffering, and physical weakness must not deprive human life of value. Human life should be respected as it is; its value should not be graded according to its subjectively assessed quality. A belief was expressed that the mother, some time after or perhaps soon after having spent a few weeks with her ill child, will be happy that she did not kill as she planned, but she let the child peacefully die under the care of the medical personnel of the neonatal intensive care unit (NICU). An abortion would have caused much greater suffering to the child. Demonstrations took place in front of the Polish embassies in London and Budapest. In Poland and abroad, in the second half of the year 2014, about 35 conferences on bioethical issues, the conscience clause, abortion, euthanasia, and dignity of life took place, to which I was invited. Television programs and press materials in Great Britain, Ireland, Australia, Germany, France, Holland, Denmark, the Czech Republic, Romania and Ukraine also appeared. I was invited to give a lecture at the conference of the International Federation of Catholic Medical Associations (FIAMC) in Manila in the Philippines.

The world is witnessing the process of depriving evil of its distinguishing features. Evil has been culturally tamed. In the past, it made the Holocaust possible; now it is assuming the form of mass crimes of abortion. I was fired quite ruthlessly and the whole situation bore the hallmarks of persecution. The aim was to demonstrate with my example to other doctors, nurses and midwives what they risk by applying the Decalogue and the principles of natural law in the sensitive and socially important practice of reproductive medicine. It was a warning for all health care employees who would decide to

apply ethical standards to their professional decisions. If firing a well-known professor is so easy, what could stand in the way to doing the same with a doctor or midwife not willing to conform? Those in power have achieved their aim by using a method which can be called management by fear. It is a well-known fact that fear kills the dignity of man, who is then more susceptible to manipulation. Recently, in one Polish city, an abortion was performed by Caesarean section, in fear that performing this procedure too far into the pregnancy could involve professional or criminal liability. The mother was thus exposed to the risk involved in a surgical procedure. In another Polish city, the court prohibited the defendant to say that in the local hospital, where eugenic abortions are performed, children are killed. It is a shame that the court did not suggest another term—one more politically correct, such as annihilation or neutralization of children.

The government's prime minister considered it appropriate to express his opinion on my case—a negative one, of course. I cannot say I feel distinguished by this fact. However, it proves the importance that the ruling circles attach to bioethical issues and their determination to deal—not in a liberal way, but just the opposite: ruthlessly—with those who want to practice their profession and follow their vocation in agreement with their conscience and, at the same time, with the views of 70% of the country's population. On the whole, the ruling circles are very willing to carry out whatever comes to us from Brussels *[considered to be the de facto capital of the European Union]* and they obediently implement it just like their predecessors did in response to the orders they received from Moscow. But it is not clear why they take no notice of resolution 1763 of the Parliamentary Assembly of the Council of Europe, adopted in 2010, which states that "no person, hospital or institution shall be coerced, held liable or discriminated against in any manner because of a refusal to perform, accommodate, assist or submit to an abortion, the performance of a human miscarriage, or euthanasia or any act which could cause the death of a human foetus or embryo, for any reason."

Ethics, morality, the principles of the Decalogue, and natural law do not always go hand in hand as statutory law. "Conscience" is a secular concept, enriched with moral imperatives of faith. It is an inseparable attribute of humanity and a characteristic of human nature only, encouraging man to do good and avoid evil (Tadeusz Tołłoczko). The conscience clause is a legally guaranteed possibility of refusal to perform an imposed obligation by citing religious or moral beliefs. It is a globally recognized right of every person—thus, also a doctor—supported by the Constitution of the Republic of Poland. The Polish Medical Code of Ethics emphasizes that "in order to perform their duties, the doctor should maintain freedom of professional actions in keeping with their conscience and contemporary medical knowledge." The source of freedom of conscience is not statutory law, but a person's constitutional rights. In 1993, the Constitutional Tribunal *[in Poland]* recognized the autonomy of ethical norms in relation to statutory law. It adjudged that "legal norms should have axiological legitimization, whereas ethical norms do not need legal legitimization." In the justified criticism of paternalism in the doctor-patient relations, the doctor's autonomy is often eliminated. Now, the doctor

is expected to fulfill all of the patient's wishes, even those not justified by his or her health-related needs. Nowadays, a model of morally and religiously neutral doctor is preferred, a doctor without a system of values and conscience, someone like a service agency carrying out orders: conceiving a child, selection, abortion, relieving pain, doing away with discomfort, shortening life.

Doctors are sometimes used to control the demographic development, "create" people, give and execute death sentences, carry out a patient's preferences, and as a tool of ideology. The conscience clause is most often cited in the above-mentioned medical procedures, which exceed the doctor's vocation and the essence of the profession.

It needs to be said categorically that a doctor is not for hire for any work. The doctor is in the service of life, not death. Interrupting human life is not in keeping with the essence of the doctor's profession. By acting against his or her conscience, the doctor loses the appropriate relationship with the patient and the appropriate relationship with himself or herself. Perhaps, for performing abortions, new specialists should be hired, and medical executioners—thanatologists—trained. And doctors should be left in peace. We should also remember the words of St. John Paul II: "a nation that kills its own children is a nation without future."

In Poland, the conscience clause is also discussed in relation to prescribing contraceptives. It is recognized by the Polish Medical Code of Ethics, but according to the Ethics Committee of the Polish Academy of Sciences, the doctors' conscience clause can be applied to abortion only. One can ask if prescribing contraceptives is a medical procedure helping to maintain health and life, or if it rather serves only personal needs which are related to lifestyle and not related to healthcare. It seems that doctors in my country who want to observe the principle of a clear conscience and do not want—in the name of ethical principles—to observe the statutory law do not receive adequate help and support, which they have a right to. They face difficulties with work and specialization studies, are exposed to ostracism of some in their professional community, excessively and unjustly punished, ridiculed, pushed to the margin, forced to leave the profession or to compromise their conscience.

No possibility to specialize in gynecology and obstetrics for doctors referring to conscientious objection will lead to a situation where the rights of women who would like to be treated by a doctor sharing their moral values will not be respected (Open letter to the members of the European Council from FIAMC, 21 September 2010). We are asking ourselves questions if the law can impose on doctors behaviors contradictory to ethics and ethos of the profession and to its duties; if such behaviors can be imposed by a patient, and if a doctor's actions should be assessed by moralists, ethicists, or lawyers. After all, even the best ornithologist cannot fly.

It is comforting and encouraging that the intense attack against me has awakened the dormant, or rather desensitized, consciences of many people, as well as their emotions and feelings. People have understood how important it is in many cases to adjust the

statutory law to natural law and ethical principles. It also seems that this case has helped to expand the awareness of how important it is to defend human life at its every stage.

Therefore, besides the understandable—in this situation—sadness related to the loss of my job and professional position, as well as stress and sometimes doubt, a feeling of satisfaction and happiness prevails in me. People's intense reaction, discussions in the press, on the radio and on television on the essence of humanity, parenthood, vocation of man, human dignity, and the essence of abortion are positive results of this story. Enormous friendliness, far exceeding hate, towards me personally, gives me joy and compensates for the discomfort. Perhaps evangelization is involved in it too.

I hope that my colleagues—gynecologists—will also wake up and follow a different and better path, for their own good, and for the improvement of health of present and future mothers and their children.

The Impact of Physician Compromise

Philip Ney, M.D.;* Marie Peeters-Ney, M.D.**

The two major medical-ethics struggles of our day (abortion and euthanasia) have an impact on Christian physicians regardless of their stated beliefs. Those Christian physicians who have participated in these practices may experience regret. A voluntary survey of physicians and spouses was offered to unselected participants at the CMDS Annual meeting, resulting in 54 responses. Of these responses, 65% were male, 36% were married at least once, 8 were single and 8 were spouses of physicians. The median age was 51-60. There were 15 family physicians and the remainder physicians of other specialties. The questions were about performing abortion and euthanasia as a physician, and perceived effects of that decision to participate.

Abortion Acceptability

The overwhelming majority (93%) of physician responses said that abortion should almost never be done. 5% the physicians indicated it could be done to save a life and one said that unplanned pregnancy would be a valid indication for abortion. The overwhelming majority (89%) indicated that there were no real psychiatric indications.

* President of International Hope Alive Counselling Association (IHACA). He founded Mount Joy College where people from all over the world come to be training in Hope live counseling. This counseling process is specifically designed to reach adults who suffer from the combined deeply damaging effects of childhood mistreatment and pregnancy losses. He graduated in medicine from The University of British Columbia and trained as a child psychiatrist and child psychologist at McGill University, University of London, and the University of Illinois. As an academic and clinician of more than fifty years, he has done extensive research into child abuse. He has taught in five universities in four countries (including Hong Kong and New Zealand). He has inaugurated and directed three child and two adolescent psychiatric units.

** Pediatrician in hematology-oncology in both Canada and France. After meeting Professor Lejeune in 1985, she joined his research team and worked with him on the metabolic consequences of chromosomal imbalances. After his death in 1994 she continues as Medical Director of the International Foundation for Genetic Research (The Michael Fund). Since 1992 Dr. Peeters-Ney has worked with her husband to train counselors throughout the world to deal with the damage caused by abuse and abortion. Together they founded IHACA with branches in 27 countries. She has a special interest in children affected by the abortion decision of a parent and by being part of an abortion culture.

Abortion Safety

Regarding the safety of abortion for the woman, 67% of respondents thought that abortion was not safer than a full term pregnancy, 26% thought that it might under some circumstances be safer than a full term pregnancy and 4% thought that abortion was safer than full term pregnancy.

Abortion Referral

54% of physicians in the survey had never referred patients for an abortion. 17% said that "I did when I was younger." Reasons for referral: HIV positivity, rubella infection, pleading from the patient.

43% of physicians had patients who initially desired abortion, but after counselling, did not proceed with abortion.

72% of physicians had never performed an abortion. 4% described being directly involved in the abortion procedure. Of physicians who had been present for an abortion, but not performed the abortion, 52% reported "just watching", 7% reported being "lied to" about the abortion prior to involvement in the procedure and 11% reported assisting.

Rights of the Child

Survey participants were asked what the first right of a child should be. 64% indicated that the first right of a child is the right to exist; followed by right to be loved (11%), right to be in a family (4%) and the right to be wanted (2%).

When asked explicitly if the first right of a child is to be wanted, 24% agreed, 48% disagreed, the rest were unsure.

When asked whether the rate of child abuse changed since abortion was legalized, 48% indicated it had increased since abortion legalization, 16% felt it had not changed, 3% indicated decrease, and 15% did not know.

Euthanasia

Responses to the question of participation in euthanasia were

- 22% of physician respondents indicated that they had performed euthanasia.
- 28% indicated that they had assisted with euthanasia
- 31% indicated that they had observed euthanasia

Compromise During Practice

Since Hippocratic medicine and Christian ethic both forbid the performance of abortion and euthanasia, the question was raised about whether or not physicians felt they had compromised their beliefs or personal conduct during their practice of medicine. On a visual analogue scale, 52% indicated "7 plus" or "compromised many times." 5% indicated that they had never compromised.

Among those who reported compromising their beliefs, 33% reported that the compromise had "huge" implications. Only 7% felt the compromise had "no effect."

Discussion

It is difficult to avoid compromise in a demanding world, where compromise of principles is expected for financial and academic success. The impact of this compromise on physician thinking and subsequent practice is an area worth investigating as it affects subsequent patient care. Questions that need to be explored are:

- The relationship between being forced to observe an abortion / euthanasia and later performance of an abortion/euthanasia.
- The relationship between ability to articulate one's principles and the tendency to compromise beliefs under pressure.
- The relationship between family history of compromise (e.g. being a sibling abortion survivor in a family who aborted one or more children) and the tendency to later compromise.
- The results of compromise on the ability of the physician to later practice according to their stated beliefs.
- What help is there for physicians who feel they have compromised their beliefs and/or ethics.
- Does it help physicians to post a statement of their ethics where patients can read it before agreeing to accept treatment by that physician?
- Is there a compromise creep starting with observing an abortion or euthanasia.

These questions are important in understanding the impact of medical training on the character formation of both physicians who practice according to a Hippocratic Ethic, and those who don't.

Since there appears to be a tendency for physicians to gradually alter their ethics ("creeping compromises"), beginning with such innocent sounding experiences as watching an abortion or doctor assisted death, God loving physicians need to have better, closer support from seniors who have been tempted, but did not succumb.

Post Abortion Survivor Syndrome

Definition

In 1979 Dr. Philip Ney discovered and described people with a unique constellation of signs and symptoms whom he called abortion survivors. The malaise they suffer is called the post abortion survivor syndrome (PASS). Post abortion survivors are all those individuals who could have been aborted but mere chance or the fact that they were wanted saved them from termination. Examples are: people who were born in a family where a sibling was aborted (with a mother struggling with her own guilt/grief and anger and often an absent father), people whose parents told them they should have been aborted, or people born in a country where the majority of children are aborted. A large part of the population is therefore affected by a number of deep conflicts that result in symptom often confused with depression, anxiety or psychosomatic complaints. There are numerous manifestations and expressions of PASS conflicts in contemporary art, literature, music and movies.

Conflicts

Abortion survivors suffer from a number of deep psychological conflicts. These are:

- existential guilt, feeling deep quilt for existing when siblings were aborted with conflicts about their intrinsic right to exist (their existence depended solely on their being wanted),
- Self-doubt, uncertain about who they are and especially their sexual identity,
- Anxious attachments, difficulties making secure attachments to mate or children.
- Ontological guilt, feeling guilty for not utilizing their gifts and opportunities
- Inability to trust and ask questions because of pseudo-secrets.
- Anger that they were robbed of a guilt-free childhood, that they have no intrinsic value and do not know who they are supposed to become.
- Sense their worth is determined only by other's approval.

Abortion survivors construct their own protective bubble where they are their own masters They live in a closed, unreal, dehumanized world, communicating with code words and through cyberspace, cut off from their emotions, in a world full of "pseudo-secrets. They are dehumanized, "disincarnated." They are constantly trying to please, to adapt and to "compromise". It is beyond the scope of this presentation to discuss all the facets of this widespread existential cancer. It affects the majority of people in the world and explains the growing turmoil and anxiety better than any other factor.

Importance in Ob/Gyn

Numerous groups, therapy sessions, private conversations and research studies have confirmed our impression that there are a number of conflicts which will surface in an ordinary ob/gyn practice.

1) *Evolving face of PAS*.

- Profound dehumanization of those growing up in an abortion culture.
- PASS: disconnection between emotions and events, life in a sealed protective bubble.
- PASS begin to show symptoms of PAS after the survivor issues have been dealt with.
- Antidepressants have placed a chemical gag on women and interfere with normal grieving.

2) *Natural family planning*. In a private conversation Dr. Evelyn Billings (Natural Family Planning) used this expression, "There are women that do not live in their bodies" to characterize a whole generation of women.

3) *Fertility*. Many PASS conflicts are tied with fertility issues: the quest for power, the need to always be in control, the dislike of children….I. There are numerous people who had infertility issues which resolved after the person had dealt with the PASS conflicts. They then became open to life.

4) *Gender identity issues* trying to life a life for the aborted sibling of the opposite sex.

5) *Promiscuity* (search for the missing sibling and trying to get close with any kind of body contact.)
6) *Marital issues*. Repetitively re-enacting the unresolved conflicts of parents by choosing the right/wrong partner.
Numerous conflicts interfere with a healthy marital situation: Cut off from emotions, fusion versus communion, difficulties in attachments. Trickery, seduction power and control, the need to "have" in order to have the right to be, difficulties making commitments, anger… ambivalent, complicated relationships with their own parents…
7) *Substance Abuse*. Trying to mute the intense obsessive mental turmoil from trying to comprehend how ones parents could kill your sibling.

References

Ney, P.G. (1983). A Consideration of Abortion Survivors. *Child Psychiatry Hum Dev* 13, 168-179.

Ney, P.G. & Peeters-Ney, M.A. (1998) *Abortion Survivors*. Victoria, Canada, Pioneer Publishing.

Peeters-Ney, M.A. & Ney, P.G. (2005) Harry Potter: the archetype of an abortion survivor. *Catholic Insight*.

Ney, P.G., Sheils, C., Gajowy, M.(2010) Post-Abortion Survivor Syndrome. *J Prenatal and Perinatal Psychology and Health*, 25,107-129.

Brain Development in Adolescents: New Research – Implications for Physicians and Parents in Regard to Medical Decision Making

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Objectives:

Provide Overview of Adolescent Brain Development

Adolescence is a time of rapid physical growth and should be the healthiest time of life. However, morbidity and mortality rates increase 200-300% between childhood and late adolescence, primarily due to initiation of high risk behaviors, including alcohol and drug use and sexual activity. Shakespeare understood the cause of these behaviors and described teens' brains as "boiled."

Sequential MRIs demonstrate the immaturity of the early adolescent brain with complete maturation and myelination not apparent until approximately 25 years of age. Many factors beside age affect brain development, including genetic control, environmental effects, nutrition, activity, and parenting. 1/3 to ½ of our 30,000 genes are involved with the development and regulation of the nervous system, so genetics does play a major role. However, studies demonstrate that genetic expression can be influenced by the environment and that change will be passed on to offspring, so that acquired traits can be inherited by subsequent generations – through "epigenetics."

Changes in Specific Lobes

Every lobe of the brain is immature in the young adolescent, but the frontal lobe has received most attention. The frontal lobe is the CEO of the brain, determining most aspects of learning, moral intelligence, abstract reasoning, judgment and strategizing, and since this area is immature, adolescents do not have the same ability to reason and make decisions as young adults.

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The cerebellum, now known to be important in navigating complicated social situations, is the last area of the brain to mature, which explains why adolescents often have difficulties understanding subtleties of social and emotional interactions.

Influence of Hormones

Risk-taking is a normal part of adolescence and is due mainly to neurotransmitters and their effects on the developing brain. Dopamine is the main hormone that is involved in the reward system of the brain, and dopamine levels are higher in adolescents than in adults, allowing teens to more easily become addicted. However, teens often require more excitement in order to generate dopamine production, so may participate in more high-risk behaviors.

Detrimental and Long-lasting Effects of Alcohol and Marijuana Use

The hippocampus, responsible for learning and memory formation, is also immature, and is an area of the brain exquisitely sensitive to the damaging effects of alcohol and marijuana exposure. The younger the age at exposure, the greater the damage, the more long-lasting the effects, and the more likely the teen is to become addicted. Adolescents who start experimenting with marijuana early have a documented 8 point decrease in IQ as adults, compared with those who never used marijuana. Binge drinking causes the most damage, but even small amounts of alcohol alter the function of the hippocampus and ability to learn and recall.

Discuss Criteria Essential for Medical Decision Making

The legal requirements for informed consent are extensive – the "decision must be informed, including information about risks and benefits of alternative treatments, the decision must be voluntary or free from coercion and the individual must be competent."[1]

The standards for competence are even more complicated, requiring the individual to demonstrate appreciation of information, capacity for abstract reasoning, ability to prioritize abstract variables, take a future time perspective, while incorporating personal values and ethics without inappropriate influence from society or friends. It is uncertain as to whether even mature adults can meet all these requirements, let alone an adolescent whose frontal lobe is not yet mature.

The American Psychological Association constructed conflicting definitions of adolescent maturity, stating teens are developmentally immature when arguing to abolish the death penalty for adolescents, but are competent and mature when consenting to abortion.[2]

Understand the Implications of the Immature Adolescent Brain on Medical Decision Making

Given that every area of the adolescent brain is immature and that the neurotransmitters are overly active, it is extremely difficult to argue that adolescents are capable of independent medical decision making without parental involvement.

Demonstrate Benefit of Parental Involvement

Because the adolescent brain is immature, the parent must become the teen's brain – providing assistance with problem solving, interpretation of events, judgment, protection from danger, and virtually every area of life. Many studies document the benefit to adolescent development when the teen is "connected" to parents and has a good relationship with parents.[3] This includes parental involvement in medical care and pregnancy-related decisions.

Appropriate medical care can ONLY be provided within the context of the patient's medical and family history which often only parents can provide. Parents can also help assure the adolescent understands all options, medical procedures, and can follow the adolescent for possible complications.

There is no study that documents adverse outcomes due to parental involvement laws prior to an adolescent's abortion – there is no evidence of an increase in child abuse, an increase in illegal or unsafe abortions, nor a significant delay in obtaining abortions. The Henshaw and Kost study which is the most cited and used by the American Academy of Pediatrics to support confidentiality is misquoted and actually shows that only 1 – 2% of adolescent girls suffered violence due to parental notification, rather than the 30% often cited.[4]

Judicial bypass is available in all states that require parental involvement to protect the small number of teens who fear retribution. Judicial bypass has been carefully evaluated and does NOT cause a delay in abortion – in fact, in one study, teens utilizing the judicial bypass process had their abortions earlier in pregnancy.[5]

In addition, parental involvement laws have been shown in some studies to change adolescent behavior, decreasing sexual activity and lowering the incidence of STIs. In one study, abortion rates fell by 13.6% after enactment of a state parental involvement law without an increase in birth rates, indicating adolescent behavior was impacted.[6]

Provide an Alternative Confidentiality Conversation

The confidentiality statement required when providing sexually related health care to adolescents places the physician in a position of creating conflict and dissension between the parent and teen, rather than building connectedness. It also tells the adolescent that the physician will collude with the teen to deceive the parent – a distressing message to provide to adolescents who need the protection of their parents.[7]

Consider the following addition to the confidentiality message provided to teen and parent together:

- The person who loves you the most is sitting here with you - and is available to you 24 / 7
- I am not here for you 24 / 7
- If you ask me to keep something confidential – I will (and I must),
- BUT because this is so important
- I will be encouraging you to talk with your parent
- If you would like, I will help you talk with your parent

References

[1] Ambuel B. and Rappaport J., "Developmental Trends in Adolescents' Psychological and Legal Competence to Consent to Abortion," *Law Hum Behav* 1992; 16:129-154.

[2] Steinberg L, Cauffman E., et al., "Are adolescents less mature than adults?: Minors' access to abortion, the juvenile death penalty, and the alleged APA 'flip flop'," *American Psychologist* 2009; 64:583-594.

[3] Resnick M.D., Bearman P.S., et al., Protecting Adolescents From Harm – Findings From the National Longitudinal Study on Adolescent Health, *JAMA* 1997; 278:823-832.

[4] Henshaw K.S. and Kost K., Parental involvement in Minors' Abortion Decisions, *Fam Plan Persp* 1992; 24:196-210.

[5] Joyce T., Parental Consent for Abortion and the Judicial Bypass Option in Arkansas: Effects and Correlates, *Persp Sex Reprod Health* 2010; 42:168-175.

[6] New M.J., "The Effect of Parental Involvement Laws on the Incidence of Abortion among Minors," *Insight* by Family Research Council. September 24, 2008.

[7] Ross L.F., Adolescent sexuality and public policy: a liberal response, *Politics and the Life Science* 1996; 15 (1): 13 – 21.

OPTIONS for Clinical Intervention in Sexual Decisionmaking

Freda M. Bush, M.D., FACOG*

As Far As We Can Tell, Two Powerful Brain Events Always Occur with Sexual Experience:

- Attachment (bonding) to the sexual partner
- Desire for repetition of sex acts (addiction)

Sex may not always lead to permanent attachment or uncontrolled addictive behavior because of multiple other influences (family, faith, control of actions by higher brain centers, etc.) But observations of brains with new imaging techniques and of behavior suggest that sexual experience can have a powerful brain impact.[1] PET scans can identify specific areas of the brain involved when a person is interested in another person, but cannot distinguish between lust and love. Only time and other behaviors can reveal the difference.[2]

- Lust is a powerful emotional state and can cause people to do things that they would not ordinarily do, often for self-gratification.
- "Early love" is a powerful emotional state, which can last several months and cause people to think of doing things they would not ordinarily do.
- Mature love is the deep, abiding love of a couple that stays together and follows the healthy evolution of "early love." It is the stability of this mature love on which marriage, home, & family depend.[3]

A separate brain area for pain has also been identified. The brain lights up in the same area if it's physical pain, like a broken bone, or emotional pain, like a broken relationship.[4]
Emotional Consequences of Sexual Activity with broken relationships:

- Pain and suffering from broken relationships
- Fear, confusion about romantic feelings
- Altered self-esteem

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- Sense of betrayal and abandonment
- Guilt, depression and emotional rollercoaster
- Impaired ability to form healthy long-term relationships

Broken bonding may explain a large percentage of adolescent depression. According to a national survey of teen health, girls who were sexually active were three times more likely to be depressed than those who were abstinent. Suicide is attempted more often by sexually active teens than those who have not had sex: three times more often by girls and eight times more often by boys.[5]

Sex & Depression – College Students

- 30% of students reported they felt so depressed that it was sometimes hard for them to function.
- 6% of students reported seriously considering attempting suicide at least once during the past year and 1.3% had actually attempted suicide.[6]

Damage to the Human "Bonding" Ability

- Individuals who have had multiple sexual partners prior to marriage are more likely to divorce when they do marry than individuals who did not have multiple partners prior to marriage.
- Couples who cohabit before committing to marriage are more likely to divorce when they do marry than couples who did not cohabit.[7]

Young Women Are More Vulnerable to premature sexual activity. They are much more likely to be pressured for sex[8] and their behavior decisions can be influenced unconsciously.[9]

- **By pheromones.** Young women are sensitive to pheromonal concentrations as little as 1/100th of a drop. These powerful chemicals influence desire for sex, and cause the young woman's mood to brighten and mental focus to sharpen, increasing propensity to sexual behavior.
- **By release of oxytocin with sexual activity.** Oxytocin not only makes them "bond" it can also make them "trust". More women than men say their beloved's faults don't matter much to them and women score higher on the test of passionate love.

The Emotional Truths

Fifty percent of teen relationships break up within six months of beginning a sexual relationship. Many teens report two weeks is common length of relationships. This has spawned the concept of "Hooking up" = sex without relationship. Hooking up results in unhealthy molding of the brain. More sex partners may lead to attachment difficulty. Brain molding that result from incomplete or unhealthy attachments is a threat to one's emotional and physical health. The philosophy that teaches that the sex act can be separated from our emotions, our minds and the rest of what we are as humans is a dangerous threat to our young people.[10]

Factors Influencing Sexual Debut[11]

- **Peer Influences.** Teens who think their peers are sexually active debut significantly earlier. The risk of sexual debut significantly higher for teens with sexually experienced friends who believed that they would gain their friends' respect by having sex[12]
- **Parental Influences.** When asked what is *most influential factor* regarding sexual decision making teens cite *parents* most often. When asked what would be most helpful to reduce teen births teens cite "*more open conversations with parents*" more than any other answer
- 87% want a pro-abstinence message from society.
- About 60% of sexually experienced teens wish they had waited.

Factors Influencing Delay of Sexual Debut Until Marriage

- **Perceived advantages of delaying sexual debut:**
  1. Free to focus on personal development (education, work, leisure, travel, etc.)
  2. No financial costs
  3. Available to everyone
  4. Encourages individuals to build healthy relationships not confused by sexual involvement[12]

Defining Sexual Activity: "What is sex"?

- Sexual activity is defined as bodily contact meant to give or derive sexual gratification.[13]
- Anal sex and oral sex are sex, and mutual masturbation is sexual activity; all 3 are not abstinent behavior, and all 3 are risky.[14]

Dangers of Early Sexual Activity

Teens who are sexually active at an early age are at risk for increased:[15]

- STIs
- nonmarital pregnancy and birth
- single parenthood
- poverty
- depression
- suicide

Sexually transmitted infections

- At least 1 in 4 teen girls (all teen girls) aged 14-19 has an STI. But this risk is stratified by culture:
  1. ~1 in 2 African American girls
  2. ~1 in 5 Mexican-American girls
  3. ~1 in 5 Caucasian girls
  4. 2 in 5 sexually experienced teen girls aged 14- 19 have an STI[16]

- Mutual Masturbation carries a known risk of transmission of Herpes, HPV and syphilis. There is a theoretical but unknown risk of HIV infection.
- Oral Sex carries a known risk of Herpes, HIV, HPV, syphilis, gonorrhea and chlamydia. Hepatitis transmission is unlikely.
- Anal Sex carries a known risk of HIV, Hepatitis B, HPV and Herpes infections as well as gonorrhea, syphilis and chlamydia.
- Chain of transmission via partners and partners' partners.
- Research on the risk reduction effectiveness of condoms has provided inconsistent results, at times showing some risk reduction and other studies showing some increased risk.[17]

Teen Births US Trends in Teen Births, 1940-2010

- Teen Birth Outcomes: Consequences for Teen Mothers[18]
  1. More likely to live in poverty
  2. Less likely to complete high school
  3. Less likely to attend college
  4. More likely to remain a single parent.
- Teen Birth Outcomes: Consequences for Teen Fathers[19, 20]
  1. More likely to drop out of school
  2. More likely to have poor involvement with their children
  3. More likely to have decreased economic stability, income, and occupational attainment
  4. More likely to engage in substance abuse and illegal activity
  5. More likely to conceive children with multiple women
- Teen Birth Outcomes: Consequences for the Child[19, 20]
  1. More likely to score lower in math and reading into adolescence
  2. More likely to drop out of high school
  3. More likely to experience abuse/neglect
  4. More likely to enter the foster care system
  5. Males are more likely to end up in prison

Screening for STIs

Dr. John Douglas, former director of the CDC's division of STD prevention said: "Screening tests are underused in part because many teens don't think they're at risk, but also, some doctors mistakenly think STDs don't happen to the kinds of patients they see." What are the facts:

- Teens & young adults have poor condom use rates. (Condom use at last sex)[21]
  1. 15-19 year olds: 66% of males and 44% of females
  2. 20-24 year olds: 53% of males and 31% of females
- Adolescents engage in high-risk sexual behaviors[22]
  1. 47% of HS students have had sex
  2. 6% had first sex at <13 years of age
  3. 15% of sexually. active students have had 4 or more partners

4. >30% of sexually. active students used drugs/alcohol before last sex
- Young adolescent females are particularly susceptible to STIs

Delay of Intercourse Reduces Number of Partners

Adolescents who start having sex at younger ages typically have more lifetime sexual partners[23]

- Number of lifetime sexual partners is a risk factor for STDs, including HIV
- Sexual debut at:
  1. 13-14 = average of 14 lifetime partners
  2. 15-18 = average of 7 lifetime partners
  3. 19-20 = average of 5 lifetime partners
  4. 21-25 = average of 2 lifetime partners
  5. 26+ = average of 2 lifetime partners

Should individuals be counseled about sexual activity?

Yes. It's a health issue, like smoking, alcohol, etc. Sexual activity is a greater health risk for an adolescent, while they are an adolescent, than smoking.

- Healthcare Provider Counseling : In the clinical setting, screening for risk behaviors, followed by brief advice and assistance can reinforce healthy behaviors or encourage needed behavior change for tobacco use, alcohol consumption, eating behaviors, exercise behaviors, certain sexual practices.
- Patients see physicians as credible information sources. Example from smoking cessation interventions:[24]
  1. Physician advice is associated with >66% increase in quit rates
  2. Intensive intervention (↑ time and ↑ sessions) yielded improved quit rates

Encouragement for Healthy Sexual Behavior for Unmarried Individuals

- encourage those who are not sexually active to continue without sexual activity until marriage.
- encourage those who are sexually active to stop sexual activity until they are in a lifelong mutually monogamous relationship – such as marriage

Barriers for Clinicians to provide sexual activity counseling

- Lack of time
- Lack of reimbursement
- Lack of appreciation for the magnitude of the problem
- Belief that clinicians have little ability to impact sexual behavior of patients
- Lack of tools and/or skills
- Lack of a plan

Sexual Behavior Inventory: Enables update of sexual involvement at a glance, in a non-threatening form. This can be completed at each visit. It can help guide discussion.[25]

- History and contact detail - "Any type of sexual activity now or in the past: genital, mouth to genital, genital to anal, hand to genital."
- Multiple sexual partners?
- Previous STI or pregnancy?
- Contraceptive use?
- Same gender sexual activity?

The 5 A's: An Organized Counseling Approach: Ask-Assess-Advise-Assist-Arrange[26]

Step 1: Ask

- Step 1: Ask each individual about sexual activity at every visit . Use understandable language. Don't make assumptions--ask the questions.
- Mechanism must fit the practice.
  1. Via interview? If so, who does the interview? When does the interview occur? How does data get recorded in the medical record?
  2. Via questionnaire/inventory? If so, who will distribute and instruct the patient? Who will review data? How does data get recorded?
- If not previously sexually active, reinforce delaying sexual debut as a healthy behavior.
  1. Point out benefits of not engaging in sex
  2. Reinforce healthy behavior: "I want to compliment you on your choice not to be sexually active. You won't have to worry about catching a sexually transmitted infection, getting pregnant (or getting someone pregnant), or having your feelings hurt if things don't work out."
- If previously sexually active, gather more data:
  1. Which sexual activities?
  2. The gender of sexual partners?
  3. The number of sexual partners?
  4. Previous STD/STI?
  5. Treatments?
  6. Current symptoms?
  7. Previous pregnancies? outcomes?

Step 2: Assess

- For each sexually active individual, assess the health risks and assess the patient's readiness to change -- attempt to identify a current stage of change. Use probing questions to assess the adolescents readiness to change.
- What does the individual know about the risks?
- Does the individual feel a need to change?
- Previous change attempts?
- Obvious motivations not to change?

A Framework for Assessing Transtheoretical Model of Behavior Change: Stages of Change[27]

1. **Pre-contemplation.** "I don't see the need to change." These individuals may respond to increasing their awareness with education, feedback and confrontation.
2. **Contemplation.** "I need to change but I'm not ready yet." These individuals are planning to make a change within the next 6 months. Help them by re-emphasizing the benefits of change and helping them make a plan with a timeline.
3. **Preparation.** "I know I'm at risk and I need to do something. I'm planning to quit within the next 3-6 weeks." Help them with plan details, problem solving, contingency planning and planning the first step.
4. **Action.** " Here I go! I'm making the effort to change." These patients need support and concrete suggestions, contingency management, counter conditioning, stimulus control and a helping relationship..
5. **Maintenance.** "Now that I've made the change, I don't want to fall back into those old habits." These patients also need support and suggestions.

Among those involved in risky behaviors:(27)

- 40% are precontemplators
- 40% are contemplators
- 20% are in the preparation stage

Step 3: Advise

- Advise each sexually active individual to stop his/her risky sexual behavior
- Voice appropriate concern for current & future health
- Make the message personal
- Be direct; don't equivocate or apologize
- Be directive, but not judgmental

Step 4: Assist

When the individual is willing to attempt to quit:

- Offer your help, or offer to enlist a trusted adult
- Refer to local organizations
- Offer supportive materials
- Explore potential problem areas
- practice delivering "the news"
- problem situations
- replacement behaviors
- Help individual identify appropriate rewards

When the patient is unwilling to attempt to quit, Probe for a reason:

- Ask, "Why not?"
- Ask, "What would it take…?"
- Offer help should they change their minds

- Offer supportive materials
- If you recommend risk reduction strategies, use them only as temporary measures—behavior change is the goal
- Use STI screening to emphasize your prevention message
- Risky behavior increases chances of STIs
- Screening is necessary for "at risk" populations
- Many professional societies and governmental agencies have screening guidelines
- US Preventive Services Task Force guidelines are included here:

Screening for Chlamydial Infection

1. Summary of Recommendations: The U.S. Preventive Services Task Force (USPSTF) recommends screening for chlamydial infection for all sexually active non-pregnant young women aged 24 and younger and for older nonpregnant women who are at increased risk. Grade: A Recommendation.
2. The USPSTF recommends screening for chlamydial infection for all pregnant women aged 24 and younger and for older pregnant women who are at increased risk. Grade: B Recommendation.
3. The USPSTF recommends against routinely providing screening for chlamydial infection for women aged 25 and older, whether or not they are pregnant, if they are not at increased risk. Grade: C Recommendation.
4. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for chlamydial infection for men. Grade: I Statement.
5. http://www.uspreventiveservicestaskforce.org/uspstf/uspschlm.htm
6. Adolescents and adults who are not at increased risk for HIV infection. Grade: C Recommendation.
7. The USPSTF recommends that clinicians screen all pregnant women for HIV. Grade: A Recommendation.
8. http://www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm

- When to screen
  1. After any new sex partner
  2. After partner has had a new sex partner

Step 5: Arrange for appropriate follow-up

- A return visit to discuss test results, perform additional exam and testing, involve another trusted person, deliver the message again: REPITITION & PERSISTENCE
- A phone call
- A follow-up letter

Counseling Clients about Behaviors: the Basics

- Behavior change is a process with predictable stages

- The process is not necessarily linear
- Relapse is common
- One's chances for successful behavior change increase with the numbers of change attempts

Two approaches to counseling

- Traditional action-oriented programs
  1. Allow rapid counseling
  2. Based on a single health message
- Stage of readiness oriented program
  1. Health message tailored to stage of readiness
  2. Based on patient's/ client's responses to assessment questions

Suggestions for an Office Plan

- Educate office staff
- Enlist office staff involvement
- Develop a plan
- Obtain and use materials

OPTIONS Model of Sexual Risk[28]

The OPTIONS model consists of three prevention categories, including:

- Primary prevention, defined as encouraging sexually inactive adolescents to refrain from sexual activity;
- Secondary prevention, a novel addition to the sexual assessment framework, defined as teaching social and emotional skills to encourage sexually active adolescents to reestablish sexual boundaries; prevention programs specifically focused on secondary needs do not exist and little is known about specific skills required to reestablish boundaries. Emphasis must be placed on increased identification of adolescents and young single adults who choose to take a "time-out" from sexual activity (secondary abstinence). Secondary prevention services may be related to the broader domains of emotional intelligence such as interpersonal skills, intrapersonal skills, communication, stress management, adaptability.
- Tertiary prevention encouraging sexually active adolescents to engage in safer sex practices. The assessment of tertiary risk includes three questions providing a rough estimate of tertiary risk:
  1. Condom use,
  2. Birth control use,
  3. Number of sexual partners

Although the OPTIONS framework is a working model that requires additional research, the simple idea of asking adolescents about their "satisfaction" or cognitive decisions regarding their sexual actions will ultimately improve the tailored nature of clinical sexual risk assessment to improve the effectiveness of their prevention and intervention efforts.

Take Home messages: Adolescents Need Adult Guidance

- Until the mid-twenties young people do not have the physical brain capacity to make fully mature decisions[29]
- We abandon adolescents to the impossibility of mature decision making if we just give them information and then say "do what you think is best" (this reality applies through the mid 20s)
- Parental Guidance is Key… Parents, physicians (mentors and other caring adults) can fill in the part of adolescents' brains that are not yet formed and can help them follow the "best road."

The Options for Sexual Clinical Interventions can be a powerful effective adjunct to parents, health providers and educators for caring authoritative counsel and guidance to adolescents and young adults gradually decreasing with age. It can help young people make good decisions especially those who are not satisfied with their sexual behavior to help them make healthier decisions to get a healthier result in all areas of their lives.

References

[1] Giedd, JN, Blumenthal, J et al, Brain Development During Childhood and Adolescence: A Longitudinal Study, *Nature NeuroScience* 2, no 10, 1999.

Weinberger DR, Elvevag B, Giedd JN, *The Adolescent Brain: A Work in Progress*,Wash, DC: National Campaign to Prevent Teen Pregnancy; 2005.

[2] Strauch, Barbara, *The Primal Teen*, New York, Random House, 2003; Leckman, JF, *Preoccupations and Behaviors Associated with Romantic and Parental Love*. Child and Adolescent Psychiatric Clinics of North America. 1999.

[3] Janice,K. Kiecolt-Glaser et al., "Psychoneuroimmunology: Psychological Influences on Immune Function and Health," *J of Consulting and Clinical Psychology*, 2002.

[4] Naiomi I. Eisenburger, "The pain of social disconnection: examining the shared neural underpinnings of physical and social pain," *Nature Reviews Neuroscience*. 13, 421-434. (June 2012).

[5] Hallfors DD. 2005. *Am J Prev Med*; Rector RE, et al. *Sexually Active Teenagers Are More Likely to be Depressed and to Attempt Suicide*, Washing DC: The Heritage Center for Data Analysis, The Heritage Foundation, 2005

[6] American College Health Association Survey, 2013

[7] Kahnetal 1991, *J of Marriage and Family*; 2Lee, et al, *1995 Demography*;[3] Rhodes, 2009, *J Fam Psychol.*

[8] Kaiser Family Foundation Survey, 2002.

[9] Havlicek, et al, "Women's Preference for Dominent Male Odour: Effects of Menstrual Cycle and relationship Status," *Biology Letters*, 2005.

[10] Hahn, et al, *J of Fam Med*, 1991; 11 *SIECUS Sexuality Education Guidelines*, 2004.

[11] *Most Sexually Active Teens Regret Having Sex*, NCPTP (National Campaign to Prevent Teen and Unplanned Pregnancy), 2012.With One Voice.

[12] Upadhyay UD, Hindin MJ. *J Adolesc Health*. 2006; 2. Sieving RE, et al. *Perspect Sex Reprod Health*. 2006.

[13] McIlhaney, J, Bush, F, *Hooked: New Science on How Casual Sex is Affecting Our Children* (Chicago: Northfield Publishing, 2008).

[14] Horan PF, Phillips, J, Hagen N. The meaning of Abstinence for College Students.l. *J HIV/AIDS Prev and Educ for Adolesc and Children*, 1998;2(2):51-56.

[15] Forhan, S. E., Gottlieb, S. L., Sternberg, M. R., Xu, F., Datta, S. D., McQuillan, G. M., et al. (2009). Prevalence of sexually transmitted infections among female adolescents aged 14 to 19 in the United States. *Pediatrics*, 124(6), 1505-1512.

[16] *Id*.

[17] a. Ahmed S, Lutalo T, Wawer M, et al. HIV incidence and sexually transmitted disease prevalence associated with condom use: a population study in Rakai, Uganda. *AIDS*. 2001; 15(16): 2171-2179.

b. Baeten JM, Nyange PM, Richardson BA, et al. Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. *Am J Obstet Gynecol*. 2001; 185(2): 380-385.

c. Celentano DD, Sifakis F, Hylton J, Torian LV, Guillin V, Koblin BA. Race/ethnic differences in HIV prevalence and risks among adolescent and young adult men who have sex with men. *J Urban Health* 2005; 82(4): 610-621.

d. Weller SC, Davis-Beaty K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database of Systematic Reviews* 2002, Issue 1. Art. No.: CD003255. DOI: 10.1002/14651858. CD003255.

e. Detels R, Visscher BR, Jacobson LP, et al. Sexual activity, condom use, and HIV-1 seroconversion. In: Voeller B, Reinisch JM, Gottlieb M, eds. *AIDS and Sex: An Integrated Biomedical and Biobehavioral Approach*. New York: Oxford University Press; 1990: 13-19.

f. Martin ET, Krantz E, Gottlieb SL, Magaret AS et al. *Arch Intern Med.* 2009;169(13):1233-40. Erratum in: Arch Intern Med. 2010; 170(11):929.

h. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis.* 2002; 29(11): 725-735.

j. National Institute of Allergy and Infectious Diseases. *Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention. June 12-13, 2000, Hyatt Dulles Airport, Herndon, Virginia*. Bethesda, MD: National Institute of Allergy and Infectious Diseases; 2001.

k. Pinkerton SD, Abramson PR. Effectiveness of condoms in preventing HIV transmission. *Soc Sci Med*. 1997; 44(9): 1303-1312.

m. Samuel MC, Hessol N, Shiboski S, Engel RR, Speed TP, Winkelstein W, Jr. Factors associated with human immunodeficiency virus seroconversion in homosexual men in three San Francisco cohort studies, 1984-1989. *J Acquir Immune Defic Syndr*. 1993; 6(3): 303-312.

n. Saracco A, Musicco M, Nicolosi A, et al. Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. *J Acquir Immune Defic Syndr*. 1993; 6(5): 497-502.

p. Vaccarella S, Franceschi S, Herrero R, et al., and the IARC HPV Prevalence Surveys Study Group. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(2): 326-333.

q. Wald A, Langenberg AG, Krantz E, *et al*. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med*. 2005; 143(10): 707-713.

r. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev.* 2002; (1): CD003255: 1-22.

s. Winer RL, Hughes JP, Feng Q, *et al*. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med*. 2006; 354(25): 2645-2654.

t. Wong ML, Chan RK. A prospective study of pharyngeal gonorrhoea and inconsistent condom use for oral sex among female brothel-based sex workers in Singapore. *Int J STD AIDS*. 1999; 10(9): 595-599.

u. Hocking J, Fairly CK. Associations between condom use and rectal or urethral chlamydia infection in men. *Sex Transm Dis*. 2006;33(4):256-8.

v. Warner L, Stone KM, Macaluso M, Buehler JW, Austin HD. Condom use and risk of gonorrhea and chlamydia: A systematic review of design and measurement factors assessed in epidemiologic studies. *Sex Transm Dis* 2006; 33(1):36-51.

[18] Kirby, D. (2007). *Emerging Answers 2007: Research Findings on Programs to Reduce Teen Pregnancy and Sexually Transmitted Disease*. Washington, D.C.: National Campaign to Prevent Teen and Unplanned Pregnancy.

[19, 20] Bronte-Tinkew, J. Burkhauser, M., Metz, A. (2008). Elements of Promising Practice in Teen Fatherhood Programs: Evidence-Based and Evidence-Informed Research Findings on What Works . National Responsible Fatherhood Clearinghouse, Gaithersburg, MD. National Campaign to Prevent Teen and Unplanned Pregnancy. Why It Matters: Teen Pregnancy and Responsible Fatherhood.

[21, 22] CDC 2012. YRBS, MMWR.

[23] Heritage Foundation 2003.

[24] Fiore, MC. 2008. *Clinical Practice Guidelines*. US DHHS.

[25] Stine,C and Mann, J; *Clinical Interventions Model*, Medical Institute, 2008.

[26] Prochaska JO[1], Velicer WF., The transtheoretical model of health behavior change, *Am J Health Promot*. 1997 Sep-Oct;12(1):38-48.

[27, 28] DeRoche-Lusczakoski, K.K., & Rue, L.A. (2011). The Options model of sexual risk assessment for adolescents. *Journal of Health Promotion Practice*.

[29] McIlhaney, J, Bush, F, *Hooked: New Science on How Casual Sex is Affecting Our Children* (Chicago: Northfield Publishing, 2008).

The Myth That Abortion is Safer Than Childbirth: Through the Looking Glass

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I. Abortion Mortality: Mythology and Methodology

Recent publications continue to put forth the same un-scientific and unsubstantiated claim that "The risk of death associated with childbirth is approximately 14 times higher than with abortion."[1] However, a comparison of abortion mortality and maternal mortality is complicated by methodological problems:

- Incomplete reporting (Abortion Data Unreliable)
- Definitional incompatibilities
- Voluntary data collection
- Research bias
- Reliance on estimations
- Political correctness
- Inaccurate/incomplete death certificates
- Failing to include all causes of death such as suicide
- Incomparability with maternal mortality statistics

II. Incomplete Reporting: (Abortion Data Unreliable)

There are no federal reporting requirements for abortion in the United States.[1,2] Only 26 states require providers to report.[3,4] And the data provided are estimates:

"Many state health departments are able to obtain only incomplete data from abortion providers, and in some states, only 40-50% of abortions are reported."[5]

The CDC collects maternal mortality data in 2 separate systems:

- National Vital Statistics System (NVSS)
- Pregnancy Mortality Surveillance System (PMSS)

For example 1995-97 NVSS reported 898 deaths while the PMSS reported 1,387 deaths. Only 54% reported in both systems.[6] Due to the incomplete nature of the data collection, CDC cautions medical professionals not to make comparative statements on

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data. In other words, these data sets cannot be used to calculate comparative safety of abortion, nor an accurate abortion mortality rate.

Guttmacher Institute (GI) is only other reporting body. Guttmacher data is voluntary, not reliable and politically motivated.

Abortion is systematically underreported with:

- < ½ reporting abortions in face-to-face interviews.[7]
- No fetal death certificates-never appear in maternal mortality calculations.
- Most women (2/3's) never return to abortion clinics with complications-therefore not reported as abortion complications.[8]

III. Mortality Definition Issues

The World Health Organization (WHO) uses 7 different methods to estimate maternal deaths.[9] Pregnancy status is not routinely reported in death certificates. It has been estimated that 50% of cases of maternal death certificates did not report pregnancy.[10] Various methods and terminology are as follows:

- Maternal deaths (by WHO)-death of woman while pregnant or within 42 days of termination of pregnancy, irrespective of duration/site of pregnancy. (Does not include suicide, homicide,accidents)
- Late maternal deaths are defined as "the deaths of a woman from direct or indirect obstetric causes more than 42 days but less than 1 year after termination of pregnancy."
- Pregnancy-related deaths-includes those from direct and indirect causes defined as "Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death."
- Direct obstetric deaths-"those resulting from obstetric complications of the pregnant state (pregnancy, labor, puerperium).
- Indirect obstetric deaths- ". . .those resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy."
- Pregnancy-associated deaths-developed by Centers for Disease Control and Prevention and with Maternal Mortality Special Interest Group of ACOG: Death from any cause during pregnancy or within 1 calendar year of delivery or pregnancy termination, regardless of duration or anatomical site. (Includes accidents, homicide and suicide related to pregnancy)
- Another way to define mortality is using a national case-fatality rate, which is the number of known legal induced abortion-related deaths per 100,000 reported legal induced abortions.
- But calculation of this number assumes all deaths are identified from all causes up to 1 year post-abortion, which is not true, and therefore the numerator is inaccurate. Also, the total number of abortions (denominator) is not known. Therefore, it is impossible to calculate this number reliably, without a reliable numerator or a reliable denominator.

- Also this calculation uses only 2 criteria in identifying maternal death:
  - Medical causes of death
  - Timing of the pregnancy-related death

IV. Mortality Measurement Issues

Maternal mortality is usually defined as:
Number of maternal deaths during a given period per 100,000 live births during same period, or
Number of maternal deaths in give period per 100,000 women of reproductive age during the same time period.

Difficulties are evident in following:

A. There are gross difficulties inherent in measuring maternal mortality and definitions regarding precisely what constitutes a death due to pregnancy vs birth.
B. There is lack of consensus regarding how long after pregnancy resolution a death is linked to the pregnancy.
C. The two national sources of abortion statistics (CDC and Guttmacher Institute) are plagued by underreporting to a huge degree.
D. For various reasons (incomplete records, lack of fetal death records), deaths due to abortion are often not recorded as resulting from the procedure with only the immediate cause of death (embolism, sepsis, and hemorrhage) provided.
E. Women experiencing life-threatening health complications from abortion go to hospital's ER's and are not usually seen by abortion doctors and thus their deaths not counted as abortion related.
F. Abortion related deaths from (from physician complications of the procedure) are usually reported as maternal deaths.
G. The death statistics tabulated for abortion focus on "uncomplicated" abortion, whereas statistics for childbirth incorporate complicated deliveries (c-sections). Comparing uncomplicated delivery to uncomplicated abortion shows the risk of dying from abortion is twice that of uncomplicated vaginal delivery.[11]
H. Available statistics do not address the long-term and less direct causes of death associated with abortion and childbirth. Risk of death associated with abortion increases over time (due to substance abuse, cancer, pregnancy complications, suicide) while that of term pregnancy show lessened risk. The present definitions of maternal death within 42 days of delivery will find those deaths due to full-term pregnancies. So, national data compares deaths associated with term deliveries to deaths associated with deaths from abortion at any point in pregnancy. This will give an inappropriate comparison group, as the appropriate comparison would be to compare the gestational age specific risk of abortion to the alternative of continuing the pregnancy at that gestational age.

IV. Mortality Measurement Issues

Maternal mortality is determined by dividing maternal deaths by live births as opposed to pregnancies. Deaths by ectopic pregnancy, molar pregnancy, miscarriage, and stillbirth are all included in the numerator but not the denominator. CDC notes that 40% of deaths occur in the other non–live birth category. This over-inflates the maternal mortality. This means that the live-birth mortality is actually only 60% of the reported maternal mortality.

Maternal mortality and abortion statistics are not analogous. Abortion statistics are by trimester. Live birth mortality ought to do the same. Statistics done by trimester find that mortality in abortion:

14.7/100,000 at 13-15 weeks;
29.5/100,000 at 16-20 weeks;
76.6/100,000 at > 21 weeks.[12]

Comparisons without regard to gestational age are flawed: Deaths during the first 6 weeks of pregnancy (when maternal morbidity and mortality are highest) are classified as maternal deaths and placed together with deaths due to birth and delivery. This is inappropriate since the intended outcomes are unknown. Women who reach the common point of awareness of pregnancy and make decision to abort (approximately 6 weeks) have already survived beyond the period of pregnancy's greatest risk. Abortions do not typically occur very early and are impossible > 9 months of gestation when most of the maternal deaths in the maternal mortality statistics occur. Therefore, valid gestational period comparisons must be done in the latter half of 1st trimester (after 6 weeks) and through the end of the third trimester.

During 2nd and 3rd trimesters, the abortion related mortality equals and then exceeds that of childbirth (childbirth-approximately 8-10/100,000).[12]

V. Abortion versus Childbirth-Evidence

Induced abortion is the 5th leading cause of maternal mortality in the U.S.[13]

Excluded from the abortion statistics are:

- suicide,
- avoidable deaths due to injuries, accidents, substance abuse, and contributory/cumulative disease states

A U.S. study spanning 8 years in California found in 2002:

- 62% increase in all cause deaths
- 154% increased risk in suicide[14]

A Finnish study in 1997 found:

- Deaths rates 4 times higher after abortion compared to childbirth up to 1 year.[15]

Subsequent studies in Finland showed:

- Maternal mortality-childbirth 28.2/100,000
- Abortion mortality-83.1/100,000 or 3 times higher[16]
- 6 times higher risk of suicide.[17]

Morgan et al. in UK found 8.1/1,000 suicide attempts in aborting patients versus 1.9/1,000 suicide attempts in those giving birth.[18]

Chang et al. in 2003 found 3 most common causes of maternal mortality in abortion:

- Infection (33.9%)
- Hemorrhage (21.8%)
- Embolism (13.9%)
- Deaths from hemorrhage 8 times higher and from infection 9 times higher in abortion compared to live-birth[19]

VI. Recent Mortality Evidence

"Imagination is the only weapon in the war against reality."
Cheshire Cat to Alice in Alice in Wonderland

Carroll et al. 2011 found the maternal mortality rate to be 8-10/100,000 live births in England, Wales,and Scotland (nations with same liberal abortion philosophy as U.S.).[20] In contrast, Carroll et al. 2011 found the maternal mortality rate to be 1-2/100,000 in the Irish Republic (where abortion is illegal) in the same time frame.

Note that the rate in England, Wales and Scotland is almost same rate of maternal mortality of 8.8/100,000 live births in U.S. quoted by Raymond and Grimes in 2012 article.

The Raymond and Grimes abortion mortality rate of 0.6/100,000 is simply non-sense and not supported by good national database information, not estimates.

Koch et al. 2012 demonstrated in their study of maternal mortality in Mexico (abortion illegal) the fundamental issue with "estimation" when they found a 10-fold overestimation of maternal mortality without record linkage.[21] In fact, Mexico actually saw a decrease in maternal mortality from 1.48 to 1.14 /100,000 live births with no abortion.[21]

Koch et al. 2012 also found in a 50 year analysis of Chile's maternal mortality covering 2 epochs: 1957-1988-abortion legal and 1989-2007-abortion illegal[22] that the legal status of abortion had no relationship to the reduction in maternal mortality in Chile- but was significantly related to better care and education.[22]

Coleman et al. 2012 reviewed the mortality rates in Denmark for the 25 years from 1962-1993 with over 1 million women with complete reproductive outcomes: (Live births, Abortions, Miscarriages).[23] The authors noted an increased risk of death for women who aborted, demonstrating a dose related effect of abortion with mortality:

- 45% increased risk with one abortion
- 114% increased risk with 2 abortions
- 191% increased risk with 3 abortions

The authors also found:

- 6-fold increase risk death if never became pregnant vs delivered a term baby

Contrary to the belief that childbirth has excess mortality compared to abortion, the authors compared maternal death rates with a live birth compared to an abortion and found a decreased risk of death for live birth outcomes:

- Death rates reduced by 108% for 2 births
- Death rates reduced by 63% for > 3 births

Conclusions

- Accurate data are lacking the U.S. due to poor quality data collection and estimates.
- Linked database data demonstrates an increased maternal mortality in abortion compared to live-birth .
- A comprehensive, objective database with reproductive outcomes is sorely needed.

References

[1] Grimes DA. Estimation of pregnancy-related mortality risk by pregnancy outcome, United States, 1991-1999. *Am J Obstet Gynecol* 2006;194:92-93.

[2] Saul R. Abortion reporting in the United States. *Fam Planning Perspect* 1998;30:244-47.

[3] Guttmacher Institute. *Abortion reporting requirements. State Policies in Brief*. 2009; 12 September.

[4] Jones RK, Zolna MRS, Henshaw SK, Finer LB. Abortion in the United States: Incidence and access to services. *Perspect on Sexual and Repro Health* 2005;40(1):6-16.

[5] *Id*.

[6] MacKay A, Berg CJ, Duran C, Chang J, Rosenberg H. An assessment of pregnancy-related mortality in the U.S. *Pediatric & Perinatal Epidemiology* 2005; 19:206-14.

[7] Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: An analysis of the 2002 National Survey of Family Growth. *Studies in Family Planning* 2007;38:187-197.

[8] Picker Institute. *From the patient's perspective-quality of abortion*. 1999. Boston, MA.

[9] World Health Organization. *Maternal mortality in 2005-estimates developed by WHO, UNICEF, UNFPA, and The World Bank* 2007.

[10] Horon I, Underreporting of maternal deaths on death certificates and the magnitude of the problem of maternal mortality. *Am J of Public Health* 2005:95: 479.

[11] Lanska J, Lanska A, Rimm A. Mortality from abortion and chilldbirth. *JAMA* 1983;250:361.

[12] Barlett LA, Berg CJ, Shulman HB, Zane SB, Green CA, Whitehead S, Atrash HK. Risk factors for legal induced abortion-related mortality in the United States. 2004; *Obstet Gynecol* 103:729-37.

[13] Kaunitz AM. Causes of maternal mortality in the United States. *Obstet and Gynecol* 1985;65:605-612.

[14] Reardon DC, Cougle J, Ney PG, Scheuren F, Coleman PK, Strahan T. Deaths associated with delivery and abortion among California Medicaic patients: A record linkage study. *Southern Medical Journal* 2002;95:834-41.

[15] Gissler M, Kauppila R, Merilainen J, Toukomaa H, Hemminki E. Pregnancy associated deaths in Finland 1987-1994: Definition problems and benefits of record linkage. *Acta Obstetricia et Gynecologia Scandinavica* 1997;76:651-57.

[16] Gissler M, Ber C, Bouvier-Coll M, Buekins P. *Pregnancy-associated mortality after birth, spontaneous abortion, or induced abortion in Finland* 1987-2000.

[17] Gissler M, Berg C, Bouvier-Colle MH, Buekens P. Injury deaths, suicides, and homicides associated with pregnancy, Finland 1987-2000. *European J of Public Health* 2005;15:459-63.

[18] Morgan C, Evans M, Peters JR. Suicides after pregnancy: Mental health may deteriorate as a direct effect of induced abortion. *Br Med J* 1997;314:902.

[19] Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, See KA, Syverson CJ. Pregnancy-related mortality surveillance-United States 1991-1999. *MMWR* 2003;52:1-8.

[20] Ireland's Gain. The demographic impact and consequences for the health of women of the abortion laws in the Republic of Ireland and Northern Ireland since 1968. *PAPRI* 2011, London, UK.

[21] Koch E, Aracena P, Gatica S, Bravo A, Huerta-Zepeda A, Calhoun BC. Fundamental discrepancies in abortion estimates and abortion-related mortality: A reevaluation of recent studies in Mexico with special reference to the International Classification of Diseases. *International J of Women's Health* 2012;4:613-23.

[22] Koch E, Thorp J, Bravo M, Gatica S, Romero CX, Aguilera H, Ahlers I. Women's educational level, maternal health facilities, abortion legislation, and maternal deaths: A natural experiment in Chile from 1957-2007. *PLoSONE* 2012;7(5):1-16, e36613.

[23] Coleman PK, Reardon DC, Calhoun BC. Reproductive history patterns and long-term mortality rates: A Danish, population-based record linkage study. *European J Public Health* 2012;1-6. doi:10.1093/eurpub/cks107.

Is Misoprostol Equivalent to Oxytocin for Postpartum Hemorrhage?

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The Problem of Postpartum Hemorrhage

Postpartum hemorrhage (PPH) is the leading cause of pregnancy-related death in developed and developing countries, followed by high blood pressure in pregnancy, anemia, infection, and malaria and dengue infection. PPH complicates 6-10 percent of all births, is estimated to be responsible for approximately 1/4 – 1/3 of all maternal deaths, and has a case fatality rate of 1%.[1] In developing countries the risk of death from PPH is estimated to be 1:100 or higher.[2] PPH is estimated to be responsible for 31% of maternal deaths in Asia, 34% in Africa, and 21% in Latin America and the Caribbean.[3]

Postpartum hemorrhage is defined as blood loss > 500 mL in the immediate postpartum period (1st 24 hrs) after vaginal or cesarean delivery (this paper will focus on PPH after vaginal delivery); other criteria include a decrease in hematocrit (blood count) or need for transfusion. PPH can occur immediately after birth or, perhaps more commonly, over the first 24 hours post-delivery, due to inadequate monitoring of bleeding and inattention to uterine massage in the recent parturient.

Cardiovascular Adaptation in Pregnancy and Mechanisms of Postpartum Hemostasis

A remarkable set of vascular, renal and coagulation system adaptations occur in pregnant women, which appear to protect against the consequences of PPH. Plasma volume begins to increase very early in pregnancy and increases until 28-34 weeks, with a parallel increase in blood volume. The total plasma volume at term is approximately 4.7-5.2 liters[4] while blood volume is 100 mL/kg, or approximately 6.5 liters in a 65 kg woman.[5] Salt retention and fluid redistribution occur during pregnancy, with an increase in extravascular fluid. As a result of increased red blood cell synthesis, red blood cell mass increases by 17-40% and the total blood volume is increased 45% over non-pregnant values. Cardiac output and heart rate increase while blood pressure de-

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creases until mid-pregnancy, when the latter begins to increase.[6] Serum levels of clotting factors increase dramatically during pregnancy.

For adequate hemostasis to occur after delivery, contraction of uterine smooth muscle is required, which enables the uterus to stop bleeding during the third stage of labor (from birth of the neonate to placental separation and delivery of the placenta). Placental separation and expulsion occur in 3 stages. The first stage involves contraction of the uterus, followed by placental separation, detachment, and expulsion. Hemostasis occurs with myometrial contraction and compression of maternal vessels, spiral artery spasm and constriction, and transient activation of the coagulation system. In contrast, inadequate uterine contraction leads to uterine atony, where the uterus is slack and non-contracted. Uterine atony is responsible for an estimated 70% of cases of PPH.[7] Thus, factors which predispose to uterine muscle fatigue or which interfere with uterine contraction are associated with postpartum hemorrhage.

Among the most common *patient* risk factors for PPH include anemia, grand multiparity (where a woman has given birth 5 or more times), long labor, twin gestation, large baby, genital lacerations, and retained clot or placenta. Of these, one of the most important risk factors is antenatal anemia, which increases mortality risk because blood loss which would be readily tolerated in a non-anemic woman can be symptomatic or fatal in a severely anemic woman. Another, often unrecognized source of blood loss is genital lacerations, which cause bleeding which cannot be controlled by increasing uterine contractions. Among the most common *health system* risk factors for PPH-related morbidity and mortality are lack of prenatal care, inadequate management of the second and third stage of labor, inadequate postpartum care, lack of access to health care facilities, and non-availability of emergency obstetrical services, including intensive care, transfusion and surgery.

Why is PPH the Leading Cause of Pregnancy-Related Death?

PPH is common, but often not prevented, recognized or adequately treated even in developed countries. It is often not easy for even a skilled birth attendant to correctly estimate blood loss during labor and delivery and diagnose PPH. In addition, a mother's hematocrit, and consequently how much blood loss she might tolerate, may be unknown when she goes into labor, especially in resource-limited settings. Finally, during the first 24 hours after birth, when most PPH deaths occur, birth attendants and those caring for parturients may not recognize that the uterus is not well contracted, perform uterine massage, or track blood loss accurately. Partly because of the cardiovascular adaptations of pregnancy, in general, postpartum women are remarkably resilient. They can tolerate significant blood loss and anemia and appear to be well, or have only subtle alterations in their vital signs and physical examination. However, once their adaptive mechanisms to blood loss are exhausted, they may suddenly die from PPH.

Consequences of Postpartum Hemorrhage

Severe PPH can lead to serious maternal injury, including shock, renal failure, liver failure, pituitary gland damage, heart failure, blood clotting disorders, adult respiratory distress syndrome, brain injury, coma, and death. Even when not fatal, PPH can have long-term effects on women's health because it can lead to chronic severe anemia. For example, where malaria is endemic, anemia is common, and women of reproductive age may be anemic prior to pregnancy before being caught up in a vicious cycle of anemia during pregnancy, increased risk for PPH-related complications, postpartum chronic severe anemia continuing into the next pregnancy, and increased future risk for PPH complications and mortality.

Hypovolemic shock (from blood loss) is the most common cause of death from PPH. The definition of shock due to blood loss is given by Mukherjee et al as follows:

> Mild shock occurs when 20% of the blood volume is lost [1300 mL], resulting in decreased perfusion of non-vital organs and tissues (i.e. bone, fat, skeletal muscle) with pale and cool skin. When 20-40% of the blood volume is lost, moderate shock occurs with decreased perfusion of vital organs (i.e. gut, kidneys, liver), oliguria and/or anuria, a drop in blood pressure, and mottling of the skin in the legs. When 40% or more of the blood volume is lost [> 2600 mL], severe shock occurs resulting in decreased perfusion of the heart and brain, agitation, restlessness, coma, echocardiogram and electroencephalogram abnormalities, and finally cardiac arrest.[8]

Severe PPH can evolve rapidly and can be difficult to treat, especially in low-resource settings. Prevention is therefore essential.

Prevention of Postpartum Hemorrhage

The first line of defense in preventing PPH is active management of the 3rd stage of labor (i.e., after delivery of the placenta). This consists of: (a) Administration of a uterotonic (a drug that enhances uterine contraction) within 1 minute of delivery of the baby, after cord clamping; (b) Gentle umbilical cord traction with uterine massage to deliver the placenta, usually within 30 minutes; and (c) Frequent uterine massage and careful evaluation of bleeding for the 1st 24 hours after birth. Evidence suggests that active management of the third stage of labor reduces the risk of PPH, maternal anemia, transfusion and the therapeutic use of uterotonic drugs. The most commonly used uterotonic drugs are oxytocin, ergometrine (or related drugs) and misoprostol.

Oxytocin as a hormonally active component was discovered in 1906 by Sir Henry Dale in the posterior pituitary of cattle and hogs; preparations of animal pituitary-derived oxytocin began to be used in 1909 and the oxytocin molecule was identified and synthesized by Du Vigneaud in 1953. Its use became widespread in the 1970s. Oxytocin is available as an injectable solution and is light-and heat-sensitive, which means that a cold chain must be in place, including transportation, electricity, refrigeration and refrigerated storage. Oxytocin has a rapid onset of action, but a short half-life. In addition oxytocin must be given by injection, requiring proper health care worker education, availability of sterile needles, syringes, gloves and antiseptic, and medical waste disposal. In many

settings reuse of syringes and needles is common, with associated risks of blood-borne infection including hepatitis and HIV. Thus, implementation of clinical protocols using oxytocin is tied to a broader agenda for health infrastructure development.

Ergometrine and related drugs are derived from ergot, produced by *Claviceps purpurea*, a fungal contaminant of rye, wheat, millet, barley and sorghum; written records from 1100 B.C. have documented ergot's use in obstetrics.[9] Ergometrine is available in oral and injectable forms. It is an effective uterotonic due to its rapid onset and sustained duration of action, but its side effects, including hypertension and arterial and spasm, are significant.[7]

Misoprostol was discovered in the 1970s as one of a series of prostaglandins. Initially marketed in 1985 as an effective treatment for gastric and duodenal ulcer and upper GI bleeding, it was noted at that time to be a uterotonic as well. Misoprostol is available in injectable and oral (tablet) forms. The oral form does not require a cold chain, however it is sensitive to moisture and high humidity. Adverse effects are more common for misoprostol than oxytocin and include fever, nausea, vomiting and diarrhea.

Oxytocin vs. Misoprostol for Prevention of Postpartum Hemorrhage

Hofmeyr et al,[10] in a Cochrane review, found that "misoprostol did not appear to increase or reduce severe morbidity" and "did not increase or reduce death [the primary outcome studied] when used to prevent or treat PPH." Another Cochrane review noted that misoprostol was more effective than placebo for prevention of PPH, but that "Compared with conventional injectable uterotonics, oral misoprostol was associated with higher risk of severe PPH (RR 1.33; 95% CI 1.16 to 1.52; 17 trials, 29,797 women) and use of additional uterotonics… Neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonics as part of the management of the third stage of labour especially for low-risk women."[11] Furthermore, a randomized controlled trial by Tewatia et al[12] found that IV oxytocin was more effective at preventing PPH than misoprostol in institutional settings, as did a Ugandan hospital-based study.

Oxytocin vs. Misoprostol for Treatment of Postpartum Hemorrhage

Clinical trials and Cochrane reviews have noted that misoprostol is less effective than oxytocin in treating PPH.[13] In a multicountry trial studying postpartum hemorrhage among 9348 recent parturients, PPH was diagnosed in 10% of women, who were randomized to 800 micrograms of misoprostol orally or 40 units of oxytocin in 1 liter IV solution given over 30 minutes.[14] Bleeding was controlled in 90% of women given misoprostol and 96% of women given oxytocin. Additional blood loss of > 300 mL was seen in 30% of women given misoprostol and 17% of women given oxytocin. Fever (greater than or equal to 38-40 degrees Celsius), nausea, shivering and vomiting were more common in the misoprostol group.

In a 2014 Cochrane Review of PPH treatment, Mousa et al[15] found that studies reviewed for meta-analysis were underpowered to assess the impact of misoprostol on the primary outcome measures of maternal mortality, severe morbidity, ICU admission

and hysterectomy. Based on available evidence, the authors concluded that "Compared with misoprostol, oxytocin infusion is more effective and causes fewer side effects when used for first line therapy for the treatment of primary postpartum hemorrhage."

Trojan Horse?

It appears from the evidence that oxytocin is superior to misoprostol for prevention and treatment of PPH. However, in developing countries, oxytocin's use is limited by (1) its heat- and light-instability; (2) the requirement for a cold chain; (3) its parenteral route of administration which requires additional resources and education; (4) risks of syringe and needle re-use; and (5) need for medical waste disposal. Misoprostol is more stable and less expensive than oxytocin, and given orally, has been recommended for primary prevention of PPH in lower resource settings. It offers the advantages of ease of administration, low cost and efficacy. However, concerns have been raised that the use of misoprostol for this indication may be a "Trojan Horse". Misoprostol is widely used for abortion as well as induction of labor. There are concerns that liberal availability of misoprostol could lead to its inappropriate use with harm to mothers and babies. For example, a 2012 Cochrane review by Oladapo et al[16] focused on advance distribution of misoprostol at the community level for PPH prevention and treatment, for non-facility births. The authors noted that advance distribution of misoprostol has the potential to save lives where there are no other uterotonics but risks inappropriate use with catastrophic maternal and fetal results (such as for abortion and labor induction). The authors cite at least 1 report of a woman with a history of cesarean section who took misoprostol to try to prevent a second C/S, with serious injury to her baby.[17] In addition, there are no data on whether community-based use of misoprostol reduces maternal mortality.

What is the Best Consensus?

Buekens,[18] in a 2010 *Lancet* commentary, states the following: "We should avoid a confrontation between misoprostol and oxytocin. Both drugs have their place in the prevention and treatment of postpartum hemorrhage. However, oxytocin is the drug of choice, and every effort should be made to make it widely accessible, including at the community level. Misoprostol is an option when oxytocin is not available, which hopefully should become increasingly uncommon." That misoprostol must be used instead of oxytocin is diagnostic of a need to improve local infrastructure and health care provider education. Where oxytocin is not available, consideration might be given to providing misoprostol to *trained* birth attendants for use in preventing PPH, with restricted distribution. Misoprostol should also not be used for treatment of PPH in women who have already received it for prevention. Utilization of misoprostol might be considered a bridge strategy to decrease mortality from PPH while strengthening local health systems, with a view to ultimately implement routine use of oxytocin.

Heat Stable Oxytocin, Inhaled Oxytocin and New Uterotonics

Significant research effort is ongoing to develop forms of oxytocin that are heat-stable and potentially easier to use. Currently, injectable liquid oxytocin is available in a ready-to-use aqueous form that does not require dilution and mixing. However, it must be stored at 25 degrees C or lower in dark conditions, or refrigerated to maintain potency, since oxytocin degrades at temperatures greater than 30 degrees C. Other strategies to improve oxytocin's stability include incorporation of chemical buffers or metal ions into the aqueous oxytocin solution to inhibit degradation by light and heat; development of powdered preparations for inhalation; and chemical modification of the oxytocin molecule. Heat-stable powdered oxytocin (for inhalation) and aqueous oxytocin solutions (for injection) are currently being rigorously evaluated for prevention and treatment of PPH in resource-limited settings.[19-21] Carbetocin, a semisynthetic analogue of oxytocin with a long half-life (1 hour vs 10 – 15 minutes), has a side effect profile similar to oxytocin and is currently being evaluated for prevention and treatment of PPH.[22]

Conclusions and Next Steps: Important Considerations for Reducing Maternal Mortality

In isolation, the use of oxytocin and/or misoprostol will not eliminate maternal mortality due to PPH. Reductions are likely to be achieved by focusing on risk factors and on the implementation of effective, proven interventions to reduce maternal mortality. There is also clear evidence that improving women's education dramatically reduces risk of maternal mortality,[24] and this may be related to greater awareness and understanding of anemia and PPH. A comprehensive approach to improving maternal health and reducing maternal mortality will therefore include improvements in the quality and availability of obstetrical health services, through investments in personnel, training, infrastructure, capacity and supplies (including medicines, birth kits), effective use of uterotonics, and women's literacy and education. These steps are essential to eliminating as much as possible this most important cause of death in mothers.

Table 1. Evidence-based practices to reduce maternal mortality associated with PPH

Antenatal	Diagnose anemia (examine inside of eyelids, palms of hands, mouth, or check complete blood count) Diagnose and treat anemia with iron or iron-rich foods as part of prenatal care Encourage nutritious diet Identify and treat causes of chronic anemia (worms, malaria, kidney disease, malnutrition)
Intrapartum (during labor)	Provide skilled birth attendants Assess for anemia (physical examination, laboratory studies) Develop whole blood transfusion and surgical capacity Use the HAEMOSTASIS algorithm[23] in cases of PPH: • **H**= Help - Call for help • **A**= Assess - Vital signs, blood loss, and resuscitate • **E**= Etiology - Ensure availability of uterotonics, blood • **M**= Massage the uterus • **O**= Oxytocin infusion, prostaglandins • **S**= Shift to operating room—bimanual compression, anti-shock garment, especially if transfer required • **T**= Tissue and trauma injury -- exclude the latter and proceed to uterine tamponade with balloon or uterine packing • **A**= Apply compression sutures • **S**= Systematic pelvic vascular devascularization (uterine, ovarian, quadruple, and internal iliac vessels) • **I**= Interventional radiology, uterine artery embolization [where available] • **S**= Subtotal or total abdominal hysterectomy
Postpartum	Train and deploy skilled birth and postpartum attendants Practice active management of the third stage of labor Massage uterus frequently after delivery and monitor uterine firmness, bleeding and vital signs Assess for anemia (physical examination, laboratory studies) Use uterotonics Develop whole blood transfusion and surgical capacity Treat chronic anemia

References

[1] Carroli G, Cuesa C, Abalos E, Gulmezöglu AM. Epidemiology of postpartum hemorrhage: a systematic review. *Best Pract Res Clin Obstet Gynaecol* 2008;22(6):999-1012.

[2] Heat stable oxytocin: Technology Opportunity Assessment. Program for Appropriate Technology in Health [PATH], 2013). Accessed at http://sites.path.org/mnhtech/assessment/postpartum-hemorrhage/heat-stable-oxytocin/.

[3] World Health Organization (WHO). MPS Technical Update: Prevention of Postpartum Hemorrhage by Active Management of the Third Stage of Labour. Geneva: WHO; 2006. Available at: http://www.who.int/maternal_child_adolescent/documents/PPH_TechUpdate2.pdf).

[3] Jansen AJ, van Rhenen DJ, Steegers EA, Duvekot JJ. Postpartum hemorrhage and transfusion of blood and blood components. *Obstet Gynecol Surv* 2005; 60:663.

[4] Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. *Am J Obstet Gynecol* 1967; 98:394.

[5] Combs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol* 1991;77(1)69-76.

[6] Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. *Cardiology Clinics* 2012; 30(3), 317-329.

[7] Gizzo S, Patrelli TS, Di Gangi S, Carozzini M, Saccardi C, Zambon A, Bertocco A, Fagherazzi S, D'Antona D, Nardelli GB. Which uterotonic is better to prevent the postpartum hemorrhage? Latest news in terms of clinical efficacy, side effects and contraindications: a systematic review. *Repro Sci* 2012: 20(9), 1011-1019.

[8] Mukherjee S, Arulkumaran S Postpartum Haemorrhage *Obstet Gynecol and Reproductive Medicine* 19(5) May 2009 121-126.

[9] Strickland JR, Looper ML, Matthewfs JC, Rosenkranz Jr CF, Flythe MD, Brown KR. Board-invited review: St. Anthony's fire in livestock: causes, mechanisms and potential solutions. *Journal of Animal Science* 2011, May;89,5.

[10] Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. *Cochrane Database Syst* Rev. 2013 Jul 15;7.

[11] Tulçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews*, August 2012.

[12] Tewatia R, Rani S, Srivastav U, Makhija B. Sublingual misoprostol versus intravenous oxytocin in prevention of post-partum hemorrhage. *Arch Gynecol Obstet*. 2014 Apr;289(4):739-42. doi: 10.1007/s00404-013-3026-2. Epub 2013 Sep 18.

[13] Akutunda E, Siedner MJ, Obua C, Mugyenyi GR, Twagirumukiza M, Agaba A. Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in Uganda: A double-blind randomized non-Inferiority trial. *PLos Med* 11(11):e1001752.

[14] Winikoff B, Dabash R, Durocher J, Darwish E, Ngoc N, Leon W, Raghaven S, Medhat I, Chi H, Barrera G, Blum J. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomized non-inferiority trial. *Lancet* 375 (9710) Jan 2010 210-216.

[15] Mousa HA, Blum J, About El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2014, Issue2.

[16] Oladapo OT, Fawole B, Blum J, Abalos E. Advance misoprostol distribution for preventing and treating postpartum haemorrhage. *Cochrane Database Syst Rev*. 2012 Feb 15;2.

[17] Airede LR, Ukwu AE. Self medication with vaginal misoprostol in a term pregnancy: case report. *Tropical Journal of Obstetrics and Gynaecology* 2006;23(1):83-4.a.

[18] Buekens P1, Althabe F. Post-partum haemorrhage: beyond the confrontation between misoprostol and oxytocin. *Lancet*. 2010 Jan 16;375(9710):176-8. doi: 10.1016/S0140-6736(10)60066-9.

[19] Fabio K, Curley K, Guarneri J, Adamo B, Laurenzi B, Grant M, Offord R, Kraft K, Leone-Bay A. Heat-stable dry powder oxytocin formulations for delivery by oral inhalation. *AAPS PharmSciTech* 2015 1530-9932/15/0000-0001/0.

[20] Avanti C, Permentier HP, van Dam A, Poole R, Jiskoot W, Frijlink HW, Hinrichs WLJ. A new strategy to stabilize oxytocin in aqueous solutions: II. Suppression of cysteine-mediated intermolecular reactions by a combination of divalent metal ions and citrate. *Mol Pharmaceutics* 2012,9,554-562.

[21] Saving Lives at Birth: Monash University. Accessed at: http://www.monash.edu.at/news/show/new-drug-delivery-to-save-the-lives-of-women.

[22] Jin B, Du Y, Zhang F, Zhang K, Wu L, Cui L. Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. *J Mat Fet Neonatal Med* 2015 Sep 4:1-8.

[23] Varatharajan L1, Chandraharan E, Sutton J, Lowe V, Arulkumaran S. Outcome of the management of massive postpartum hemorrhage using the algorithm "HAEMOSTASIS". *Int J Gynaecol Obstet* 2011 May;113(2):152-4.

[24] Tunçalp Ö, Souza JP, Hindin MJ, Santos CA, Oliveira TH, Vogel JP, Togoobaatar G, Ha DQ, Say L, Gülmezoglu AM, on behalf of the WHO Multicountry Study Survey on Maternal and Newborn Health Network. *BJOG* 2014 Mar;121 Suppl 1:40-8.

The Neuroanatomy and Physiology of Pain Perception in the Developing Human

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The human experience of pain is one that becomes more complex with time. The cerebral cortex continues to develop for 25 years after birth, making the human response to pain as variable as each unique individual. As the cortex develops, the response to pain becomes a very unreliable indicator: there are those who over-react to or fabricate pain, and those who refrain from responding. The experience of pain, however, is so universal that we naturally intervene to prevent or minimize pain for others. We anticipate that an experience will be painful and respond accordingly.

Technological developments and experience during fetal surgeries and pre-natal interventions have provided observational data that has changed previous assumptions that pre-born children are incapable of feeling pain. These observations are consistent with those that have been made over a period of several decades, affirming that pre-born babies respond to even light touch at a very early age. They respond with aversion behaviors and movement away from stimuli (Humphrey p. 93)(Kadic p3). Surgeons who specialize in fetal surgery study anesthesia protocols to determine the safest, most effective ways to prevent the fetus from experiencing pain during invasive procedures (Tran, Sudhakaran, Myers). This in turn has raised the question of whether children who are aborted are suffering in pain as they are dying. The moral and ethical considerations of this issue become more apparent as the science is applied.

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Embryological Concepts

One of the most accomplished scientists in the study of embryology was Eric Blechschmidt, MD, (1904-1992), a German anatomist and physiologist who worked for more than forty years studying the development of the human form in the first eight weeks of life after conception. He produced more than 120 scientific papers and numerous books on the form and function of the developing human. Blechschmidt focused on the evidence presented by the embryo itself, producing more than 200,000 serial sections of embryos of different ages and sixty-four enlarged total reconstructions that have been on display at the University of Gottingen.

Dr. Blechschmidt emphasized the importance of studying the human embryo for understanding of human development. In contrast, many researchers attempt to use mammalian or amphibian models as parallels to human development, which introduces errors and misunderstandings.

One of the unfortunate scientific fallacies often repeated even today is the discredited concept of "phylogenetic recapitulation" or "ontogeny recapitulates phylogeny." This idea that the human conceptus passes through evolutionary non-human phases in its development was first purported by Haekel, and supported by drawings and data which Haekel later admitted were fraudulent (Blechschmidt). However, by the time that the fraud was admitted, the concept had become firmly entrenched in biology, and continues to be taught today. This falsely derived concept propagates the idea that the unborn human being is less than human, a concept not supported by scientific evidence.

The human being develops from a uniquely human single cell which comes into existence at the moment at which a human sperm penetrates a human egg (M. Condic). The biological knowledge we have today clearly demonstrates that no developmental phase exists that constitutes a transition from the "non-human" to the "human." That is, there is no scientific evidence for a stage in human development prior to birth in which one could claim that a being exists which is "not yet human." Human development is distinctly human and uniquely individual from conception (Blechschmidt).

Dr. Blechschmidt's observations were unique in his whole-body approach to the embryo. He considered the function of all parts of the developing embryo to parallel the structure. "The development of the central nervous system implies the simultaneous development of functioning afferent and efferent central pathways (tracts) and centers. Nothing has been found to support the idea that the function of the nervous system is added after the development of its shape and cell structure. It is the author's opinion that the function and structure develop simultaneously. The beginning of the nervous system implies the simultaneous beginning of function." (7) P.105.

Definitions of Pain

The question that all physicians have heard many times before performing a medical procedure or treatment is "will it hurt"? Doctors go to great lengths to minimize and prevent pain for their patients. Requiring proof that a patient has pain before admin-

istering necessary treatment is in opposition to the ethical training of physicians. The physician anticipates pain and protects people from it when possible.

Definitions influence therapy and protocol; therefore, the definition of pain is key to the approach physicians take in patient care (Derbyshire, #27). There are two different ways of defining pain in the literature: the subjective perception, and the objective observation (Anand), (Derbyshire), (Lee)(Guyton).

Anand noted that the I.A.S.P. Committee for Taxonomy definition of pain, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" shifts the direction of research on pain. The definition is further qualified: "Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life" (Merskey 1991) (Anand, 1996, p.3) (27, Derbyshire). The exclusive use of this definition creates a mindset that pain perception develops over time as a learned experience, thus, treatment of the immature or disabled person would be minimized, risking an inhumane approach to care of vulnerable individuals.

The *JAMA* article (Lee), often used as the authoritative paper proving that the unborn child does not feel pain, uses a psychological definition: "Pain is a subjective sensory and emotional experience that requires the presence of consciousness to permit recognition of a stimulus as unpleasant." This statement is a scientific hypothesis dependent on subjective and negative data for its conclusion. Its basis is devoid of original data and dismisses counter examples, excluding abundant scientific data on pain perception.

The basic science definition of pain is formed by objective observation: "Pain is a protective mechanism for the body. It occurs whenever any tissues are being damaged, and it causes the individual to react to remove the pain stimulus" (Guyton).

Basic Science Observations

There are three scientific classifications of pain:

1. Pricking pain is felt when a needle is stuck into the skin or when the skin is cut with a knife, or when widespread area of the skin is irritated.
2. Burning pain is felt when the skin is burned, can be excruciating, and is most likely to cause suffering.
3. Aching pain is a deep pain with varying degrees of annoyance. Aching pain of low intensity in widespread areas of the body can summate into a very disagreeable sensation.

Each of these types of pain stimuli are carried along different neurofibers in the organism:

1. Pricking pain: carried along fast Delta type A fibers.
2. Burning pain: carried along slow type C fibers.
3. Aching pain: carried along slow type C fibers.

The pricking pain pathway produces a rapid response to pain at the spinal cord level and travels to the reticular activating system (reticular formation of brainstem and intralaminar nuclei of thalamus), where the majority of the pain fibers terminate. Type

A fibers enter the spinal cord, synapse with an interneuron, cross over, and travel up in the anterolateral pathway. Very few Type A fibers travel directly to the thalamus via the spinothalamic tract, terminating in the ventrobasilar complex and posterior nuclear group. These fibers connect with neurons that synapse with the somatic sensory cortex for the purpose of localizing the pain.

The burning and aching pain pathways terminate diffusely in the reticular formation and in the thalamus, with very few connecting fibers to the cortex. It is characterized by gross localization and the ability to summate when large areas of the body are being damaged. The purpose of these pathways is to alert the individual that damage is being inflicted (Guyton, 1986, 2010 (illustration)).

Another important characteristic of pain fibers is the non-adapting nature of pain receptors: in contrast to other sensory fibers, pain receptors adapt either not at all or almost not at all. "In fact… the threshold for excitation becomes lower and lower as the pain stimulus continues, thus allowing these receptors to become progressively more activated with time." This increase in sensitivity is called hyperalgesia (Guyton, 1986, p. 593).

Pain is Directly Correlated to Tissue Damage

A variety of approaches have been used to study pain perception. The methods for eliciting perception of pain include:

1. Pricking the skin with a pin
2. Applying pressure against a bone
3. Pinching the skin
4. Heating the skin

One of the most reliable ways to measure a pain threshold is by gradually increasing heat applied to the skin. 'By far the greatest number of people perceive pain when the skin temperature reaches almost exactly 45C… Almost everyone perceives pain before the temperature reaches 47C." Across cultures this has been proven: there is very little difference in the threshold of pain perception, (Guyton 1986, p 592-593), but there are wide variations in response to pain. The point at which tissue begins to be damaged by heat is 45C, thus, the pain is correlated to tissue damage. "The intensity of pain has also been closely correlated to the rate of tissue damage by other effects besides heat," (contusion, chemical substances, infection, ischemia) (Guyton 1986, p. 594).

The threshold at which pain is perceived in contrast with the response to pain must be discerned. As the human brain learns from various experiences and training, the response to pain may change and varies greatly with the individual (Anand p. 3 1996., De Buck, p. 295).

The Sub-cortical Neurological Pathways Involved in Pain Perception

Type A and Type C pain fibers travel in the lateral division of the anterolateral pathway, remaining differentiated as fast or slow fibers. About three-quarters to nine-

tenths of all pain fibers terminate diffusely in the reticular formation and in the thalamus (these two areas constitute the reticular activating system). The reticular formation is part of the medulla, pons, and mesencephalon (Guyton).

Burning and aching pain fibers excite the RAS, thus activating the entire nervous system, causing arousal from sleep, creating a sense of urgency, and promoting defense and aversion reactions, alerting the individual that damage is being inflicted. The summation property of the pain fibers in the RAS, especially when large areas of the body are being damaged, causes the most intense suffering in human experience (Guyton, 1986, p. 596). Without the descending inhibitory pathways that develop after birth (Van de Velde, p 233), a pre-born baby is capable of perceiving unmitigated, intense suffering when it is crushed or torn, as is commonly experienced in an abortion procedure.

The pain perception functions remain in the lower centers and are not dependent on the cortex, although some modification of the pain threshold may occur (Lowery p.276, Guyton p.596). Pain impulses that enter and terminate in the lower brain centers, especially the reticular formation and the thalamus, can cause conscious perception of pain (Guyton, 1986, p. 596) (de Buck).

Chronology of Neurological Development

The neurological development of the fetus is chronicled by various researchers, noting the appearance of structures within common timeframes. Most authors agree that nociceptors appear around the lips at around 7 weeks. At this stage, however, the free nerve endings associated with pain perception have not penetrated the epidermis (Humphrey p. 128, RCOGp4). These fibers continue to develop and mature throughout the body up to 20 weeks gestation. The cortex is developing at around 8 weeks, and the thalamus enlarges rapidly between 7 and 8 weeks along with the growth of the afferent and efferent fibers, illustrating the coordinated growth of the system of pain perception. The peripheral afferent fibers are developed by 10 weeks, and the spinothalamic connections mature at 14 weeks. These fibers continue to appear as the fetus grows. Thalamocortical tracts form at 20-22 weeks, reaching the subcortical plate, and are seen projecting to the cortex at 23 weeks. Maturation of the synapses of the thalamocortical fibers is seen at 26-34 weeks. The hypothesis that the components of the nervous system begin to be functional after the appearance of the mature anatomical form conflicts with data that suggests that the function parallels or precedes structure (Blechschmidt, Humphrey).

Neurological Development of the Fetus

WEEKS	*Anatomical Structure Developed*
7-20	nociceptors
8	cortex begins to develop
10-30	peripheral afferents
7.5	spinal reflex
14-20	spinothalamic connections

20-22 Thalamocortical tracts (cortical plate)
26-34 synapses of thalamocortical fibers
(Salihajic, Anand, Van de Velde, Vanhatalo, Derbyshire, Lowery).

Arguments and conclusions in support of the hypothesis that pre-born children are incapable of feeling pain rely on the definition that pain is a psychological perception that is dependent on intact thalamocortical fibers. Therefore, using this limitation and the research showing the appearance of thalamocortical fibers at 23 weeks in fetal development, the conclusion is that the child cannot feel pain until 23 weeks at earliest (Merskey (12), Lee, et al (6), Derbyshire (11) p119, S. Derbyshire (13)). The various articles conclude that a fetus is capable of pain at different ages, from 11-26 weeks, depending on the definition used and the limitation placed on pain perception. Many authors rely on maturation of synapses as a turning point after which a pain signal may be transmitted.

In view of the consistent observations of aversion behavior at 7-7.5 weeks, it can be concluded that at this age the embryo is responding to sensory input. The thalamus is already formed, and during the seventh week the thalamus rapidly expands (Moore. p.395) in conjunction with the developing nociceptive system of the spinal cord, (Moore, p.395) demonstrating that the components of pain perception develop as a unit. Projections from the spinal cord can reach the thalamus from seven weeks gestation.

It is significant that the reflex exhibited by the embryo at 7-8 weeks is a coordinated response, not a localized reflex. The pattern-type behaviors appear earlier than more specific local responses, indicating more generalized communication by the nervous system ((Humphrey) Fitzgerald M. (17), Andrews KA, (18)). The more specific local reflexes have been noted to appear at 9.5 weeks. This is timed with the free nerve ending contact with the basement membrane of the epithelium of the lips (Humphrey p 127). The trigeminal nerve ganglion is one of the first to develop, and carries a rich supply of sensory and motor nerve fibers (Moore p. 407). Sensory nerves of the trigeminal are present in embryos as small as 2.57mm (Blechschmidt Ontogenetic p. 105). The components of the reflex arc are formed and capable of function in embryos between 6-7 weeks gestation (Blechschmidt Ontogenetic Basis…p. 103; Windle and Fitzgerald).

It is important to consider that the function developes along with the structure (Brusseau, p.20). As Blechschmidt described, the brain and spinal cord are developing functionally as a whole unit simultaneously (Biokinetics, Blechschmidt, p. 105). The principal unit of pain perception is in place and rapidly expanding at 7-8 weeks. The necessary components for pain perception are present and becoming more complex and sophisticated during the second trimester (Brusseau, p.20).

Consciousness

As the anatomical and physiological evidence demonstrates, the role of the cortex in consciousness and pain perception is minimal. "Although the cortex may elaborate the contents of consciousness, it's not the seat of consciousness." (Merker 2007). Merker, Brusseau, and Bellieni agree that consciousness is not dependent on the presence of a

cerebral cortex. These conclusions are reached by independent clinical observations of conscious behavior in individuals without a cortex (Beshkar). Infants with hydraencephaly, in which little or no cortical fibers are present, demonstrate conscious recognition, pain perception, musical preferences, and alert, wakeful behavior. These represent counter-examples to the hypothesis that consciousness requires a cerebral cortex. The data suggest rather that consciousness is a function of the lower brain centers. Further, ablation of the somatosensory cortex does not alter pain perception in adults, underscoring the anatomical implication that pain perception occurs in the lower brain centers (Brusseau, p.16), (Morsella).

Hormonal Responses

The hormonal stress response has been recently studied as a marker for adequate pain control and outcome of surgical procedures (Goldman, Gupta, Kilby, and Cooper) (de Buck, p294). Derbyshire states that "the presence of an intact HPA axis at 18 weeks gestation is a suitable conclusion, but the HPA axis is a subcortical system and so its activity is not evidence for cortical awareness or conscious pain perception (Derbyshire (11)). The stress response to invasive procedures has been examined in the fetus and is characterized by increased cortisol and B-endorphin circulation following intrauterine needling of the fetus beyond 18 weeks gestation (Giannakoulopoulos X). The hormonal and metabolic changes that follow physical injury or psychologic trauma do not include any conscious components that may accompany the stress response (Goldman RD; Gupta, p74). This is evidence that indicates that the pre-born baby is capable of perceiving pain, but it is dismissed by those who insist that the cortical connections must first be matured (ACOG; Lee).

The anatomical and physiological mechanisms of pain perception are observable in scientific studies and the accumulation of data over time reinforces the concept that pre-born children are capable of feeling pain (De Buck p. 294). Examining the arguments from the perspective that it is unlikely that pre-born children feel pain provides better understanding of the objections to consideration of protecting the pre-born. The most frequently quoted articles are reviews of previous studies (Lee, Derbyshire, RCOG) The reasoning is typically vague, or suggesting that lack of data is cause for skepticism.

The following reasons are some of those offered to oppose efforts to provide pain prevention for the pre-born:

1. Pain perception requires at a minimum mature synapses between the thalamus and cortex (RCOG; Derbyshire).
2. Limited evidence indicates that pain perception is unlikely (Derbyshire).
3. Lack of evidence of effectiveness of direct fetal anesthetic or analgesia precludes its use (Derbyshire).
4. Limited data is available on safety of the woman in the context of abortion (Lee; Derbyshire).
5. Efforts to provide pain control in the context of abortion increases the cost of care unnecessarily (Lee; Derbyshire).

6. Techniques used in fetal surgery don't apply in the case of abortion (Lee).

Discussion

In spite of the many supporting studies on fetal anatomy, physiology, and behavior, the reasoning for skepticism about fetal pain is rooted in a desire to protect the abortion industry. "Evidence regarding the capacity for fetal pain is limited but indicates that fetal perception of pain is unlikely before the third trimester. Little or no evidence addresses the effectiveness of direct fetal anesthetic or analgesic techniques. Similarly, limited or no data exist on the safety of such techniques for pregnant women in the context of abortion. Anesthetic techniques currently used during fetal surgery are not directly applicable to abortion procedures." (Lee et al.). This statement reflects a disregard for the cumulative data from research that provide substantial evidence of fetal pain perception. The supposition is that the absence of data in the context of abortion is sufficient to cast doubt on the concept of fetal pain.

According to Lee, objectives of pain control during fetal surgery are not applicable to abortion because the intention is not to help the pre-born (Lee, p. 951). "In the context of abortion, fetal analgesia would be used solely for beneficence toward the fetus, assuming fetal pain exists." (p. 952.) This statement reveals the heart of the opposition—that the pre-born baby is not given consideration as a human being. The supposed benefit to the mother or society precludes any consideration of the baby's health or experience of pain.

Rather than encouraging studies that would support or refute current data, the directive by opposition is "instead, further research should focus on when pain-related thalamocortical pathways become functional in humans." (Lee et al.). This is based on a hypothesis that has no data to support it. The anatomical evidence shows that the thalamo-cortical fibers relay information on the location of cell damage, and are not related to pain perception.

The conclusion of RCOG is that "evidence that analgesia confers any benefit on the fetus at any gestation is lacking but should be a focus of future research" (ACOG p.19). In spite of the experience and observation of surgeons who treat these pre-born children, the opposition dismiss the vast knowledge and experience that has accumulated and instead keep us focused on concepts that are confusing and based on negative data. They point repeatedly to a lack of data, without presenting valid data to prove the proposed hypothesis that a developing human is incapable of pain perception.

Conclusion

The fetus is structurally and physiologically equipped to perceive pain at a very early age, and demonstrates physiological responses consistent with pain perception. These responses are observable at 7.5 weeks and continue to develop until birth. Many of the arguments submitted against recognizing pain perception of the pre-born child are centered on a hypothesis that is already confronted with counter-examples. The rationale for opposing efforts to study pain prevention for the pre-born appears to be founded

on a need to justify practices that completely disregard the life of the baby and dismiss any possibility of suffering, regardless of the preponderance of evidence to the contrary.

References

[1] Benatar D, Benatar M. A pain in the fetus: toward ending confusion about fetal pain. *Bioethics*.2001;15: 57-76.

[2] Condic, M. "When Does Human Life Begin?" *The Westchester Institute for Ethics and the Human Person*. 2008 Thornwood, NY. Westchester Institute White Paper Series, vol 1, number 1.

[3] Glover V, Fisk NM. Fetal pain: implications for research and practice. *Br J Obstet Gynaecol*. 1999;106: 881-886.

[4] International Association for the Study of Pain. IASP Pain Terminology. 2004. *Available at*: http: //www.iasp-pain.org/terms-p.html.AccessedMay2, 2005. http://www.iasp-pain.org/Taxonomy?navItemNumber=576#Pain, accessed9/8/15

[5] *Textbook of Medical Physiology*, sixth edition, Arthur C Guyton, MD, 1981, 1986 WB Saunders Co, p. 611

[6] Lee S, JD, Ralston HJ, MD, Drey E, MD. Fetal Pain: A Systematic Multidisciplinary Review of the Evidence. *JAMA* August 24/31, 2005, vol 294:8.

[7] Blechschmidt E, MD. Gasser RF, PhD. *Biokinetics and Biodynamics of Human Differentiation.* North Atlantic Books, 1978, 2012.

[8] Merker B 2007. Consciousness without a cerebral cortex: A challenge for neuroscience and medicine. *Behavioral and Brain Sciences*. 30(2007)63-81

[9] Bellieni CV and Buonocore G. Is fetal pain a real evidence? *The Journal of Maternal-Fetal and Neonatal Medicine* (2012),1-6.

[10] Brusseau R Developmental Perspectives: is the Fetus Conscious? *International Anesthesiology Clinics*. 46:3 (2008) 11-23

[11] Derbyshire S. Fetal Pain: Do we know enough to do the right thing? *Reproductive Health Matters.* 2008; 16(31 Supplement): 117-126.

[12] *Merskey H. The definition of pain. *European Psychiatry* 1991; 6:153-59.

[13] S. Derbyshire. Can Fetuses feel Pain? *BMJ* 15 April 2006; 332:909-912

[14] Meyers LB, Bulich LA, Hess P, Miller, NM. Fetal endoscopic surgery: indications and anaesthetic management. *Best Practice and Research Clinical Anaesthesiology*. 18:2(2004)231-258.

[15] Goldman RD, Koren G. Biologic markers of pain in the vulnerable infant. *Clinical Perinatology* 2002;29:415-25.

[16] Giannakoulopoulos X, Sepulveda W, Kourtis P, et al. Fetal plasma cortisol and B-endorphin response to intrauterine needling. *Lancet* 1994;344:77-81.

[17] Fitzgerald M. The prenatal growth of fine diameter afferents into the rat spinal cord—a transganglionic study. *Journal of Comparative Neurology.*1987;261:98-104.

[18] Fitzgerald, M. The Development of Nociceptive Circuits. *Nature Reviews/Neuroscience*. Vol 6. July 2005. p. 509-520. Doi:10.1038/nrn1701.

[19] Andrews KA, Fitzgerald M. The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. *Pain* 1994;56:95-101.

[20] Moore K. *The Developing Human: Clinically Oriented Embryology.* WB Saunders Co. 1982, p. 395.

[21] Humphrey T. Some correlations between the appearance of human fetal reflexes and the development of the nervous system. *Progress in Brain Research*. 4 (1964) 93-135.

[22] Ritu Gupta MB ChB FCARCSI Mark Kilby MBBS MD MRCOG Griselda Cooper OBE FRCA FRCOG. Fetal Surgery and Anesthetic Considerations./ Continuing Education in Anaesthesia, *Critical Care & Pain J* Volume 8 Number 2 2008

[23] Windlew, . F., and Fitzgeraljd. , E., (1937); Development of the spinal reflex mechanism in human embryos. *J. Comp. Neurol.*, 67, 493-509.

[24] Anand, KJS, and Craig, K. New Perspectives on the Definition of Pain. *Pain* 1996. vol.67, p.3-6.

[25] De Buck, F., Deprest, J., and Van de Velde, M., "Anesthesia for Fetal Surgery." *Current Opinion in Anesthesiology*. 2008. 21:293-297.

[26] Sudhakaran, N., Sothinathan, U., Patel, S., "Best Practice Guidelines: Fetal Surgery." *Early Human Development* 88 (2012) 15-19.

[27] Tran, K., "Anesthesia for fetal surgery," *Seminars in Fetal and Neonatal Medicine* 15 (2010) 40-45.

[28] Derbyshire SW, Foetal Pain?, *Best Practice &Research Clinical Obstetrics and Gynaecology* (2010), doi:10.1016/j.bpobgyn.2010.02.013

[29] Mellor, D., et. al. The importance of 'awareness' for the understanding fetal pain. B*rain Research Reviews* 49 (2005) 452-471.

[30] Lowery, C. MD, Neurodevelopmental Changes of Fetal Pain. *Seminars in Perinatology* 31(2007) 275-282.

[31] Salihagic Kadic, A, Predojevic, M., Fetal Neurophysiology according to gestational age. *Seminars in Fetal and Neonatal Medicine* (2012), doi. 10.1016/j.siny.2012.05.007.

[32] Beshkar, Majid. The Presence of Consciousness in the Absence of the Cerebral Cortex. *Synapse* 62:553-556, 2008.

[33] Fitzgerald, M. *The Development of Nociceptive Circuits*. Vol 6. July 2005. P507-517.

[34] Fisk,N., FRCOG, PhD, et. al., Effect of Direct Fetal Opioid Analgesia on Fetal Hormonal and Hemodynamic Stress Response to Intrauterine Needling, *Anesthesiology* 2001;95:828-35.

[35] *Fetal Awareness: Review of Research and Recommendations for Practice*. Royal College of Obstetricians and Gynaecologists. March 2010.

[36] Blechschmidt, Erich. *The Ontogenetic Basis of Human Anatomy: A Biodynamic Approach to Development from Conception to Birth*.

Levonorgestrel "Emergency Contraception" How Does it Work?

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In 1999, the Food and Drug Administration approved Plan B as an "emergency contraceptive." Plan B® consists of the progestin hormone levonorgestrel, and can be administered in two different regimens: Levonorgestrel 0.75mg tablet within 72 hrs of unprotected sex followed by 1 more tablet 12 hrs later or Plan B One-Step® Levonorgestrel 1.5 mg taken up to 120 hrs after intercourse.

But how exactly does Plan B work to prevent a recognizable pregnancy at the end of a cycle? According to the manufacturer's website:

> If Plan B One-Step® is taken as directed, it can significantly decrease the chance that you will get pregnant. About 7 out of every 8 women who would have gotten pregnant will not become pregnant.
>
> Plan B One-Step® is one tablet with levonorgestrel, a hormone that has been used in many birth control pills for several decades. Plan B One-Step® contains a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary. It is possible that Plan B One-Step® may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb). It should not be used as regular birth control, as it is not as effective.

Yet, this description does not explain the mechanism by which recognizable pregnancy is prevented at the end of a cycle. What evidence do we have about the mechanism of action of Plan B?

Direct Evidence: Interference With the Ovulatory Process – Demonstrated in Several Studies.

Hypothetical Mechanisms:

- Interference with fertilization by affecting sperm migration – no direct evidence

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- Interference with implantation – no direct evidence according to the manufacturers testimony (Barr testimony FDA 2003)

The question pertinent to patients who do not want to destroy embryos after fertilization is: "Is there any harm to an embryo after fertilization takes place?" In other words, does the drug have any action to impair embryo development after fertilization? It is clear that post-fertilization effects were recognized as being a desirable part of the ideal mechanism of action of emergency contraceptives.[1]

> to achieve the highest possible efficacy, the ideal emergency contraceptive drug needs to act interceptively; that is, it should be capable of interfering with a physiological event that occurs after fertilization – during the period of early embryonic development prior to implantation.

The fertile phase of the menstrual cycle lasts about 6 days: five days before ovulation and the day of ovulation. That means the chances of becoming pregnant are highest in the days leading up to and including the day of ovulation. The probability of a fertilization leading to conception increases as the day of ovulation approaches. Intercourse 6 days before ovulation has a zero percent chance of fertilization leading to pregnancy; 5 days before ovulation= 10% chance; 4-3 days before ovulation = 15% chance; 2 days before ovulation = 25% chance; 1 day before ovulation = 32% chance and ovulation day = 34% chance. Coitus more than 24 hours after ovulation has a zero percent chance of fertilization. Note that prediction of ovulation is challenging, as women's cycles may vary from month to month and woman to woman. But, in answering the question of mechanism of action of an emergency contraceptive, or even the effectiveness of emergency contraceptives, timing is everything. This prompts critically important questions regarding the mechanism of action of an emergency contraceptive?

- Was the woman in the fertile window when she took the drug?
- Did the drug prevent ovulation?
- Did the drug incapacitate sperm by a cervical or sperm motility effect?
- What effect did the drug have on embryo survival and successful implantation?

Durand et al. (2001)[2] studied 45 women who had been sterilized. The first cycle was a control cycle. Women were then tested daily for the presence of urinary LH, then serum LH, estradiol and progesterone in addition to daily ultrasounds once LH had been detected. Daily serum estradiol and progesterone levels were followed until period began. Levonorgestrel-EC was given on day 10 of cycle. Results:

- LNG-EC suppressed ovulation 80% of the time when given day -5 or earlier.
- All ovulated when LNG-EC given days -4 to -2.
- Deficient progesterone levels and luteal phase deficiencies in those who ovulated.
- All ovulated when given the drug -1 to +1 with no effect on luteal phase.
- No effect on endometrial histology.

Durand et al. (2005)[3] analyzed 3 groups of women: Group 1 given LNG-EC days -4 or -3, Group 2 given drug day -1 (LH surge), Group 3 given LNG-EC day +1. The

authors looked at the long-term effects of a premature rise in progesterone on luteal progesterone and glycodelin levels. Glycodelin-A is at low levels except in the late luteal phase and prevents maternal rejection of the blastocyst. Results:

- "Levonorgestrel taken for emergency contraception prior to the LH surge alters the luteal phase secretory pattern of glycodelin in serum and endometrium."
- Levels of glycodelin-A were low at the time of implantation, preventing the suppression of mother's natural killer cells.

Palomino et al. (2010)[4] LNG-EC given the day of the LH surge only.

- Results: no effect on progesterone or factors necessary for implantation when given the day of the LH surge.
- Concluded LNG-EC had no postfertilization effect but that was only for that day of administration!

Noé et al. (2010)[5] 337 women: LMP, time of intercourse and blood work drawn on day of LNG-EC. Measured daily serum LH, estradiol, progesterone and daily U/S's to measure the follicle.

- 63.7% received the drug in the infertile time.
- 62 women were on days -5 to -1 and 86% ovulated with no pregnancies.
- 35 women took the drug the day of ovulation or after and all ovulated and there were the usual number of pregnancies.
- "this suggests that other mechanisms than suppression of ovulation prevents pregnancy in these women."

What about Sperm Function?

Yeung et al (2002)[6] – LNG-EC affects sperm function only at high concentrations in vivo.

Brito et al. (2005)[7] –LNG-EC had no effect on the acrosomal reaction in sperm in the uterus 36-60 hrs after coitus and 24-48 hrs after LNG-EC.

Do Nascimento et al. (2007)[8] – LNG-EC had no effect on sperm function or cervical penetration when tested uterine washings 36 to 60 hours after intercourse and 24 to 48 hours after LNG-EC.

Conclusion

LNG-EC does not consistently prevent ovulation unless given on the first day of the fertile window. LNG-EC appears to have no effect on sperm function or penetration of the cervix. LNG-EC's effectiveness depends on other effects on the normal survival of the embryo prior to implantation.

References

[1] Von Hertzen H, Van Look P. Research on new methods of emergency contraception. *Int Family Planning Perspectives* 22 (2) June 1996 p 62-62. *Available at* https://www.guttmacher.org/pubs/journals/2206296.pdf

[2] Durand M, Cravioto M, Raymond E, Duran-Sanchez O, Cruz-Hinojosa M, Castell-Rodriguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception *Contraception* 64 (2001) 227–234

[3] Durand M1, Seppala M, Cravioto Mdel C, Koistinen H, Koistinen R, González-Macedo J, Larrea F. Late follicular phase administration of levonorgestrel as an emergency contraceptive changes the secretorypattern of glycodelin in serum and endometrium during the luteal phase of the menstrual cycle. *Contraception* 2005 Jun;71(6):451-7.

[4] Palomino WA, Kohen P, Devoto L. A single midcycle dose of levonorgestrel similar to emergency contraceptive does not alter the expression of the L-selectin ligand or molecular markers of endometrial receptivity. *Fertility and Sterility* Vol. 94, No. 5, October 2010 1589-1594.

[5] Noe G, Croxatto HB, Salvatierra AM, Reyes V, Villarroel C, Munoz C, Morales G, Retamales A. Contraceptive efficacy of emergency contraception with levonorgestrel given before or after ovulation. *Contraception* 81 (2010) 414-420.

[6] Yeung WS, Chiu PC, Wang CH, Yao YQ, Ho PC The effects of levonorgestrel on various sperm functions. *Contraception* 2002 Dec;66(6):453-7.

[7] Brito KS, Bahamondes L, Nascimento JA, de Santis L, Munuce MJ. The in vitro effect of emergency contraception doses of levonorgestrel on the acrosome reaction of human spermatozoa. *Contraception* 2005 Sep;72(3):225-8.

[8] do Nascimento JA, Seppala M, Perdigao A, et al. In vivo assessment of the human sperm acrosome reaction and the expression of glycodelin-A in human endometrium after levonorgestrel-emergency contraceptive pill administration, *Hum Reprod* 22 (2007): 2190-5.