



## SCIENCE

### *The Risks of Oral Contraceptive Use*

According to a recent report from the Institute of Medicine (IOM), a report cited numerous times by Health and Human Services Secretary Kathleen Sebelius in her public and congressional statements on the HHS contraception mandate, the side effects of oral contraceptive use are generally considered minimal.<sup>1</sup> In fact, the IOM report makes a point of highlighting the noncontraceptive benefits of hormonal contraception, including the treatment of menstrual disorders, acne, hirsutism, and pelvic pain and the reduction of risks associated with endometrial and ovarian cancer.<sup>2</sup> However, the scientific literature is not so ready to dismiss the risks of oral contraceptive use.<sup>3</sup>

Several papers published in the past few months illustrate well the risks associated with oral contraceptive use not only for women but also for men. First, George Iatrakis and colleagues interviewed 405 female patients who had been diagnosed with breast cancer, and concluded that there was a small but significant increased risk for the disease in two patient populations (“The Role of Oral Contraception Use in the Occurrence of Breast Cancer: A Retrospective Study of 405 Patients,” *Clinical and Experimental Obstetrics and Gynecology*, 2011). Specifically, the risk is increased in (1) women who are carriers of the BRCA mutation, which can cause hereditary breast and ovarian cancer, and (2) women who have a significant medical or family history of breast, ovarian, or colon cancer and who previously used oral contraceptive pills for

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<sup>1</sup> Committee on Preventive Services for Women of the Institute of Medicine, *Clinical Preventive Services for Women: Closing the Gaps* (Washington, DC: National Academies Press, 2011), 105.

<sup>2</sup> *Ibid.*, 107.

<sup>3</sup> For a balanced summary of the risks associated with oral contraceptives, see R. Burkman et al., “Safety Concerns and Health Benefits Associated with Oral Contraception,” *American Journal of Obstetrics and Gynecology* 190.4 (April 2004): S5–S22.

more than seven years. This confirms the findings of two previous studies that suggested that women who were current or recent users of birth control pills, especially very young women, had a slightly elevated risk of developing breast cancer.<sup>4</sup> This is not surprising, since the estrogen found in combined oral contraceptives is a hormone that is known to regulate the growth of breast tissue. Higher levels of estrogen in the blood have been clearly linked to an increased risk of breast cancer in postmenopausal women.<sup>5</sup> Researchers are investigating a possible link to breast cancer in premenopausal women as well. It would not be surprising if scientists eventually discover that the higher risk for breast cancer is linked to the same biological mechanism that explains the lower risk for ovarian cancer in women who take oral contraceptives.

Next, in a surprising paper, a research team from the University of Toronto examined whether oral contraceptive use by women is associated with prostate cancer in men (D. Margel and N. E. Fleshner, "Oral Contraceptive Use Is Associated with Prostate Cancer: An Ecological Study," *BMJ Open*, 2011). Using an ecological study, they showed a strong and significant association between oral contraceptive use and the incidence of prostate cancer in individual countries throughout the world. Use of any other form of contraceptive, including intrauterine devices, condoms, or vaginal barriers, was not correlated with the incidence of prostate cancer or with mortality from it. Mechanistically, the Canadian team hypothesized that the oral contraceptive effect may be mediated by the environment: exposure to high levels of environmental endocrine-disturbing compounds like the hormones found in oral contraceptives could increase prostate cancer risk.

Third, a study published in a relatively obscure medical journal by a research team from South Africa has suggested the women on contraceptives have reduced levels of zinc, selenium, phosphorus, and magnesium in their blood (O. Akinloye et al., "Effects of Contraceptives on Serum Trace Elements, Calcium and Phosphorus Levels," *West Indian Medical Journal*, June 2011). Significantly, serum trace elements play important roles in maintaining the health of both men and women, and many have been implicated in disease.<sup>6</sup>

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<sup>4</sup>Collaborative Group on Hormonal Factors in Breast Cancer, "Breast Cancer and Hormonal Contraceptives: Collaborative Reanalysis of Individual Data on 53,297 Women with Breast Cancer and 100,239 Women without Breast Cancer from 54 Epidemiological Studies," *Lancet* 347.9017 (June 22, 1996): 1713–1727; and M.D. Althuis et al., "Breast Cancers among Very Young Premenopausal Women (United States)," *Cancer Causes and Control* 14.2 (March 2003): 151–160. There is one study that contradicts the findings of these two major research papers: P. A. Marchbanks et al., "Oral Contraceptives and the Risk of Breast Cancer," *New England Journal of Medicine* 346.26 (June 27, 2002): 2025–2032. It is not clear how to reconcile the discrepant findings of these three studies, especially in light of the robust data, discussed below, that clearly links high levels of estrogens in the blood to the development of breast cancer.

<sup>5</sup>Endogenous Hormones and Breast Cancer Collaborative Group, "Endogenous Sex Hormones and Breast Cancer in Postmenopausal Women: Reanalysis of Nine Prospective Studies," *Journal of the National Cancer Institute* 94.8 (April 17, 2002): 606–616.

<sup>6</sup>For instance, the essential transition metals—including zinc, manganese, copper, and iron—have been linked to Alzheimer's disease. A. L. Bush, "The Metallobiology of Alzheimer Disease," *Trends in Neurosciences* 26.4 (April 2003): 207–214.

Fourth, several recently published papers continue to confirm previous work showing that certain oral contraceptives cause serious blood clots. For example, a team led by Øjvind Lidegaard from the University of Copenhagen reports that the risk of developing the blood clots known as venous thromboembolisms is double for women taking contraceptive pills that contain one of the newer forms of progesterone, such as drospirenone, desogestrel, or gestodene, compared with women taking contraceptive pills that contain an older form of progesterone like levonorgestrel (“Risk of Venous Thromboembolism from Use of Oral Contraceptives Containing Different Progestogens and Oestrogen Doses: Danish Cohort Study, 2001–9,” *BMJ*, October 25, 2011). The large-scale study reviewed the hormonal contraception data and first occurrence of blood clots for all non-pregnant Danish women between the ages of fifteen and forty-nine years from January 2001 to December 2009. This involved assessing more than eight million women-years of observation. The team concluded that in women taking contraceptive pills with levonorgestrel and women taking pills with a newer form of progesterone, the risk of blood clots increased three-fold and six-fold respectively compared with the risk in women who do not use the pill. The increased risk remained even after taking account of other possible causes for the blood clots. This finding has been confirmed by another recent paper that systematically reviewed all the studies published between January 1995 and April 2010 to determine the effect of combined hormonal contraceptives administered orally, transdermally, or vaginally on the risk of blood clot formation (F. Martinez et al., “Venous and Pulmonary Thromboembolism and Combined Hormonal Contraceptives: Systematic Review and Meta-analysis,” *European Journal of Contraception and Reproductive Health Care*, February 2012).

Finally, in a paper that elicited a formal response from the International Planned Parenthood Federation, a research team from the University of Washington in Seattle has reported that hormonal contraceptives increased the risk of HIV-1 transmission in couples (R. Heffron et al., “Use of Hormonal Contraceptives and Risk of HIV-1 Transmission: A Prospective Cohort Study,” *Lancet Infectious Diseases*, January 2012).<sup>7</sup> More specifically, among 1,314 couples in which the HIV-1-seronegative partner was female—that is, couples where the woman is HIV negative and her male partner is HIV positive—rates of HIV-1 acquisition were 6.61 per 100 person-years in women who used hormonal contraceptives, compared with 3.78 per 100 person-years in those who did not use hormonal contraceptives. Among 2,476 couples in which the HIV-1-seronegative partner was male, rates of HIV-1 transmission from women to men were 2.61 per 100 person-years in couples where the woman used hormonal contraception, compared with 1.51 per 100 person-years in couples where the woman did not use hormonal contraception. Thus, the authors conclude, “Women should be counselled about potentially increased risk of HIV-1 acquisition and transmission with hormonal contraception, especially injectable methods.”

Together, these papers—and they are representative of a wide range of studies in the scientific literature—suggest that the side effects of oral contraceptives are

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<sup>7</sup> The IPPF response is available at <http://www.ippf.org/en/Resources/Statements/IPPFs+response+to+Hormonal+contraceptive+use+increases+ womens+risk+of+acquiring+and+transmitting+HIV.htm>.

not as negligible as some public health officials make them out to be. It is striking that the risks of oral contraceptive use were not really discussed in the IOM report when so much was made of their benefits.

### *The Biology of Pluripotent Stem Cells*

Two scientific papers published recently continue to uncover the biological basis of pluripotency, the ability of stem cells to develop into a wide diversity of specialized adult cells. First, a research team from Denmark, Scotland, and the United States has shown that a single molecule called Oct4 is sufficient to transform specialized adult cells into induced pluripotent stem (iPS) cells if it is allowed to turn on its target genes (F. Hammachi et al., “Transcriptional Activation by Oct4 Is Sufficient for the Maintenance and Induction of Pluripotency,” *Cell Reports*, February 23, 2012). The scientists were able to create synthetic versions of Oct4 that were much more efficient at turning on Oct4 target genes—genes required to transform adult somatic cells into iPS cells. These findings could help scientists identify new protocols for generating stem cells in the laboratory.

Next, where in the mammalian embryo do embryonic stem cells come from? A report in the journal *Nature Biotechnology* describes experiments that suggest that human embryonic stem cells arise from a particular subset of the cells that make up the inner cell mass (ICM), specifically, from the cells found in the center of the week-old human embryo called a blastocyst (“Tracking the Progression of the Human Inner Cell Mass during Embryonic Stem Cell Derivation,” March 2012). Thomas O’Leary and colleagues from Belgium and the Netherlands studied the transformation of ICM cells into human embryonic stem cells. By studying 221 plated blastocysts, they identified a unique morphological structure that they call the post-ICM intermediate (PICMI) that is necessary and sufficient to generate human embryonic stem cell lines. The PICMI can be cryopreserved without compromising its ability to generate embryonic stem cells.

Both papers highlight the tremendous progress that has been made in trying to understand the basic biology behind the stem cell discoveries that make the headlines.

### *The Evolution of Virtue and Morality*

The natural-law virtue ethics that grounds the Catholic moral tradition is only one of the ethical theories competing in the public square today. One of its principal rivals is the secular account of ethics that grounds morality in the evolutionary process that selects for beneficial adaptations that promote altruistic behavior.

Several papers published recently in the journal *Evolution and Human Behavior* highlight different aspects of this ongoing and wide-ranging research program. For example, a team of anthropologists based at Stanford University has examined the cooperative behavior of women hunters from the Aboriginal Martu tribe of Western Australia to better understand the evolutionary origins of altruism (R. B. Bird et al., “The Hierarchy of Virtue: Mutualism, Altruism and Signaling in Martu Women’s Cooperative Hunting,” January 2012). Basically, they asked the question, why do these women hunters who hunt small animals and supply half of the bush meat that their tribe consumes choose to hunt in groups rather than as individuals? They discovered both that better hunters are not more likely to pair up with hunters with whom they are related and that better hunters do not necessarily consume more even if they

acquire a larger proportion of the prey. To the authors, this suggests that cooperative behavior did not evolve because individuals had selfishly calculated that cooperation would increase their hunting success—the standard explanation for the evolution of cooperative behavior. Instead, the team proposes that cooperative activity actually acts as a signal of commitment to the common good rather than as the result of a selfish calculation that cooperation will increase yield.

Next, in recent years, psychologists have discovered the omission effect, the phenomenon that individuals often find that moral violations by omission are judged to be less wrong morally than violations by commission, holding intentions constant. For instance, people judge it more wrong to poison someone than to withhold the antidote from someone who has been poisoned, even though the intended consequences are the same.<sup>8</sup> Why do they do this? A group based at the University of Pennsylvania wanted to test a novel hypothesis: omissions are judged less harshly because they produce little material evidence of wrongdoing (P. DeScioli et al., “The Omission Effect in Moral Cognition: Toward a Functional Explanation,” May 2011). The group’s experiments confirmed their hunch: the omission effect was eliminated when physical evidence explicitly showed that an omission had been chosen by the acting person. The researchers conclude that “to reduce condemnation, omissions must not only be noncausal, they must also leave little or no material evidence that a choice was made.”

Finally, in a third study, Daniel Krupp, Lisa DeBruine, and Benedict Jones sought an evolutionary explanation for the prevalence of reciprocity in humans, where reciprocity is a mutually beneficial arrangement in which individuals repay the investments of others (“Apparent Health Encourages Reciprocity,” May 2011). In other words, why do people help each other? Or, to put it a third way, in evolutionary terms, why does the Good Samaritan help the injured traveler? Using apparently anonymous trust games, where two players have to decide either to help or not help each other financially, the research team discovered that participants were more willing to repay attractive partners who appear healthy than those who appear unhealthy. It appears that human beings want to maintain amicable relationships with people who will live longer and have more time to make the financial help worth their while.

The Catholic tradition of natural-law virtue ethics will have to incorporate these evolutionary studies and others like them into a coherent worldview that acknowledges the evolutionary origins of the natural inclinations that ground the moral life in our species. St. Thomas Aquinas worked to bring together the best science of his day—his Aristotelian patrimony—into his ethical philosophy and moral theology. We have to do the same.

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<sup>8</sup>Fiery Cushman, Liane Young, and Marc Hauser, “The Role of Conscious Reasoning and Intuition in Moral Judgment: Testing Three Principles of Harm,” *Psychological Science* 17.12 (December 2006): 1082–1089.