

The \$100 Million Question: Does NuvaRing Usage Result in Increased Cardiovascular Dysfunction?

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If you have been following current news in the pharmaceutical industry, you have likely heard about over 3500 product liability lawsuits that were filed against Merck in the past several years asserting claims arising from the use of the NuvaRing, an intravaginal contraceptive ring that releases ethinyl estradiol and etonogestrel. These claims alleged that the manufacturers failed to design and produce the NuvaRing with adequate testing and study, that use of the NuvaRing leads to injuries including blood clots, cardiovascular dysfunction, and death, and that the drug companies failed to adequately warn doctors and patients of the increased risk of blood clots posed by use of the NuvaRing. As a result of these allegations, Merck has agreed to settle with the claimants for \$100 million. But is the NuvaRing any more dangerous than other hormonal birth control options?

Studies linking hormonal contraception to increased risk of blood coagulation and other cardiovascular issues that have been widely known to clinicians and researchers since the 1990's. Hormones such as estrogen and progesterone have been shown to modulate coagulation, and hormonal contraceptive use increases the risk of venous thromboembolisms depending on the amount and type of estrogen and progesterone released [1]. For instance, women of reproductive age who use hormonal contraceptive methods are at six to eight times higher risk for venous thromboembolism than non-users, particularly in their first year of use or if they have predisposing conditions such as thrombogenic mutations [2-4].

Though hormonal contraceptive use is associated with increased cardiovascular risk, is NuvaRing use any more dangerous than other hormonal birth controls? Several comparative studies that were performed before the lawsuits against Merck gained strong momentum have reported that use of the NuvaRing leads to significantly fewer cardiovascular issues than the patch or oral pill [5-9]. When the lawsuits against Merck reached critical levels, several large-scale clinical trials were initiated to specifically examine the association of thrombosis with NuvaRing usage. The results obtained from these studies have proven to be highly controversial. A 2008 study comparing surrogate biomarkers of thrombosis in hormonal contraceptive users demonstrated that switching to the NuvaRing exhibited beneficial changes in biomarkers of thrombosis compared to use of the contraceptive pill or patch [10]. A prospective observational study examined venous and thromboembolic risk in over 33,000 women that were using either the NuvaRing or combined oral contraceptive pills. The study revealed that vaginal ring use and combined oral contraceptive pill use were associated with statistically similar venous and arterial thromboembolic risks during routine clinical use [11]. A Food and Drug Administration-funded retrospective cohort study using data from four health plans further

indicated that users of the NuvaRing showed similar thromboembolic events as those who used oral contraceptive pills [12]. In contrast to the studies mentioned above, only one research report using a statically relevant patient population has revealed a small increased risk of venous thromboses in users specifically of the NuvaRing compared to combined oral contraceptives [13]. However, this study has been heavily criticized by biostatisticians as having fundamental limitations in the way comparisons were made among current contraceptive users; namely failing to account for differential risk due to time period exposure of contraceptive use, resulting in statistical bias against all newer products. Moreover, further criticisms of this study were made public in the scientific community as the lead principal investigator of the study was on the pay role of the drug company Bayer, which is one of Merck's strongest competitors in the contraceptives industry.

What we do know is that hormonal contraceptive use increases one's risk of cardiovascular dysfunction such as thromboembolisms. However a wealth of data suggests that use of the NuvaRing is at least no worse than other hormonal birth control options with regard cardiovascular side effects. The \$100 million settle put a small dent in Merck's very deep pocket book, and the downstream effects of this settlement could be loss of pharmaceutical jobs at Merck, increased contraceptive costs, and other negative ramifications. Despite the thousands of lawsuits against Merck, the company reported \$686 million in revenue from the NuvaRing last year, up 10% from the previous year, so hopefully those effects will be minimized.

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