The below comment was submitted to the medical journal 'Circulation, Cardiovascular Quality and Outcomes' on May 26, 2016 by Lynne Millican RN, but was never published. This comment was in response to Harvard / Brigham & Women's Hospital authors' May 11, 2016 reply to Millican's April 26, 2016 published comment (article and all comments can be found @ http://circoutcomes.ahajournals.org/content/early/2016/03/29/CIRCOUTCOMES.115.002224.short#responses).

In summary, the article written by Harvard / Brigham & Women's authors ("Endometriosis and Risk of Coronary Heart Disease" - found at latter link) proposed a relationship between endometriosis and risk of coronary heart disease, yet their data (Nurses' Health Study II) did not include Lupron/GnRHa use, which is known to have multiple adverse cardiac effects. My April 26, 2016 published comment addressed the impact of lack of any Lupron/GnRHa exposure data in their study.

The authors published a response to my comment on May 11, 2016, and stated that "Lupron was approved in 1996", was not in prevalent use during the 1990s or early 2000s, and therefore "Lupron use was not sufficiently prevalent among all 116,430 nurses to allow prioritization for precise exposure collection".

These 'facts' and this conclusion could not be more wrong - hence my submission to 'Circulation, Cardiovascular Quality and Outcomes' of the following detailed, corrective, comment (which the journal declined to publish):

I wish to thank the authors for their response, and am encouraged they concur future study of Lupron/GnRHas' relationship to heart disease in women (and children) is warranted. However, several erroneous statements by the authors beg for correction - namely involving Lupron's early history of prevalent use in treating endometriosis. Given the authors reliance upon their false assumption to the contrary, their misguided conclusion that "insufficient prevalence of Lupron's use amongst the nurses' cohort [would not] allow prioritization for precise exposure collection" should be addressed and revisited.

While no supportive information is provided, the authors claim Lupron has only currently gained widespread use for endometriosis, and those US nurses who "were surgically diagnosed in the 1990s or early 2000s" would not have received Lupron because Lupron "would not have been the prominent treatment among the women from this cohort … Lupron use was not sufficiently prevalent among all 116,430 nurses to allow prioritization for precise exposure conditions".

However, Lupron's initial FDA approval for endometriosis was in 1990, not "1996" as stated by authors. Lupron's use in women was indeed prevalent in the 1990s and early 2000s; and the following information is provided to make this germane point clear to both authors and readers.

In 1983, it was noted that "a decade of investigation of GnRH and its agonistic and antagonistic analogs" had taken place, in which "intense investigation [occurred] in all species, including man" (1). (Studies using GnRHas in sheep were conducted because of "their widespread clinical use for down-regulati[on] [] in men and women" (2)). During discovery in litigation (3) related to a 1989 course of Lupron for endometriosis, 2 Boston physicians stated that in their practice, respectively, Lupron was first used in

1986 while at Brigham & Women's (4), and "it was a large number [of "patients treated with Lupron for endometriosis in 1989"]"(5).

A 1989 Industry bulletin noted "[a]lthough clinically available, GnRHas have not been approved for this usage" (6). After the FDA repeatedly warned Lupron's manufacturer ("TAP") about their "deliberate campaign to promote this product for a wide range of unapproved uses … involv[ing] a large number of detail representatives visits to ob/gyns [with] systematic promotion of gyn uses", in 1990 the FDA filed a Notice of Adverse Findings against TAP (7). Yet, the "program to indoctrinate physicians in unapproved uses of Lupron" continued (8). More than a decade later, TAP would settle civil and criminal charges with the US government (paying the then-highest fine in history - $875 million) over charges it, among others, "conspired to pay kickbacks to doctors and other customers … and offered to give things of value, including free drugs, so-called educational grants, trips to resorts, free consulting services, medical equipment, and forgiveness of debt, to physicians and other customers to obtain their referrals of prescriptions for Lupron" (9). The latter indictment pertained nearly exclusively to urologic uses of Lupron, however similar schemes were known to occur in gynecology, with enticements of $100,000 annual profit for gyn physicians who put their patients on Lupron (10). (In the early 1990s Lupron was also "a first-line therapy" for children with precocious puberty (11), and by the late 1990s Lupron had gained "widespread" use in treating fibroids (12).)

NIH's 1991 'Facts about Endometriosis' discussed GnRHas "currently being tested", with an NICHD researcher "finding good medical options without surgery" (13). The 'Endometriosis Association [EA] Newsletters' were reporting in 1991 they "ha[d] heard from many members taking Synarel or Lupron who ha[d] experienced side effects that were much stronger than they expected … severe side effects" (14). In Lupron's manufacturer's 1992 'Annual Report' it is stated "Lupron Depot 3.75 mg has achieved wide physician acceptance as a treatment for endometriosis" (15). Numerous citations can be found in medical literature throughout the 1990s whereby renowned endometriosis experts acknowledge they "commonly use Lupron for endometriosis" (16) and "it is the standard of care" (17). A front-page, 2-day investigation by the Boston Globe in 1996 (see "Lupron Misuse?") identified women reporting "severe, even life-threatening symptoms" and quoted the founder of the now-defunct 'National Lupron Victims Network' as having been contacted by "thousands" (18). By the late 1990s, Lupron-induced depression during treatment of endometriosis had been noted to such an extent that studies were underway evaluating effectiveness of concomitant antidepressants (19).

Furthermore, the parent organization of the Nurses' Health Study, Brigham & Women's, should be obliged to be well aware of Lupron's prevalent use, from its beginning, since leading Lupron research originated out of its halls - i.e., its Chief of Reproductive Endocrinology and Director of its IVF program received countless TAP grants during the 1990s to study Lupron (20), and numerous studies and publications resulted (21) - perhaps the most eye-catching being the 3 identified fraudulent Lupron studies (22), 2 of which were published and required retraction(23). In a PubMed literature search of "Lupron Brigham & Women's", there are 51 publications listed, and 33 involved female indications between the years 1987 and 1999 (24). In addition, in a PubMed literature search of "Lupron female endometriosis", 151 publications appear from the date of the 1985 NIH conference "Therapeutic applications of luteinizing-hormone-releasing hormone and its analogs" through the year 2000 (25).

Moreover, endometriosis is a known cause of infertility. In 1989, a US Subcommittee mailed a detailed survey to 224 US fertility clinics to obtain 1987 and 1988 IVF (in vitro fertilization) and GIFT (gamete intra-fallopian transfer) data on, among other variables, the number and percentage of patients treated for endometriosis (26). Although not queried within this survey, many clinics self-reported their

universal use of Lupron in addenda to the survey, i.e.; "changing to Lupron stimulation for all patients" (27); "us[ing] Lupron for all patients" (28); seventy percent of all patients are administered leuprolide" (29); "in 1988 we initiated the use of GnRH agonist for all patients" (30); "we attribute our high success rate [] to this stimulation protocol [Lupron]" (31); "Ovulation induction: … Lupron [cost =] $400.00" (32). In contrast, one clinic noted: "Promoting the Use of GnRHa (Lupron) … it remains entirely unclear that all patients need this costly and often painful [and "experimental"] approach" (33).

Other fertility clinics that did not volunteer information in this survey about their Lupron use were nonetheless also using Lupron; i.e., one of the highest volume US fertility clinics stated (within aforementioned litigation's discovery) they "began using Lupron about 1987 onward" (34), their 1989 patient brochure stated "Lupron has been successfully used in IVF programs throughout the world" (35), and their submitted IVF/GIFT survey data identifies considerable treatment for the indication of endometriosis (36). Brigham & Women's IVF clinic noted in its April 1990 'IVF Instruction Brochure' that Lupron "is only prescribed to persons with certain diagnoses", but by December 1991 this Brochure was changed to read Lupron "is widely prescribed" (37). Moreover, 1990 industry statistics documented that 97% of ART (assisted reproductive technology - IVF/GIFT) cycles in the US utilized GnRHas (38), of which Lupron was and is known to be the most frequently prescribed.

The tally of stimulated ART cycles within the 1989 US Subcommittee's survey for the 2 year period 1987 & 1988 was "26,332 stimulated cycles" (26); the latest figures available, for 2014, indicate there were 190,384 cycles (39).

Clearly Lupron enjoyed widespread use in treating endometriosis, and also in treating infertility due to endometriosis, in 1990, during the 1990s, and during early 2000s - a point which hopefully the authors can now appreciate.

Several of the authors of 'Endometriosis and Risk of Coronary Heart Disease' have also published elsewhere (40) in which reference is made to a publication reporting on an EA survey that asserted a "strong association" with endometriosis and numerous diseased states (41), however this publication failed to factor or mention that 59% of survey respondents had used Lupron/GnRHas (42). Other examples, by other authors, could be given (i.e., study asserts an association of bone density loss with the disease of endometriosis (43) while failing to mention the subjects had prior GnRHa exposure, which is known to cause bone density loss (44)). This trend is troubling.

The authors offer no supportive evidence for their statement "It is not now possible to retrospectively collect data on timing of Lupron initiation, dose and duration from its approval for use [in 1990] through 2016 with sufficient validity." Although not a participant in the Nurses' Health Study II, as an RN prescribed Lupron for (surgically diagnosed) endometriosis in 1989, I can tell you precisely when, how much and for how long my Lupron exposure was - and know of no reason to assume nurses within the Nurses' Health Study II could not do likewise.

Additionally, the authors cite elsewhere that "[t]reatment for endometriosis may include … GnRH agonists []. If any of these treatments were associated with the risk of the explored disease outcomes [i.e., coronary heart disease], then it would have the potential to act as a mediator of the association between endometriosis and this disease outcome. … In the report from our group … mediation analyses showed that part of the association between endometriosis and myocardial infarction and angina could be partially attributed to medical treatments for endometriosis" (40). In the present

response, the authors cite "about 55% of the association between endometriosis and coronary heart disease could be attributed to the treatment factors that we could validly examine in this study." Since there is no data on Lupron/GnRHa exposure available for examination, then my initial point bears repeating: any estimate of risk, without factoring GnRHa use, is flawed. How valid can findings be if they exclude the standard of care in pharmacological management of endometriosis, which has been utilized for nearly three decades?

If there is an entity that should be acutely aware of, and investigating, the potential adverse impact(s) of Lupron/GnRHas upon women's health, beginning in the 1990's, it should be Brigham & Women's, the Nurses' Health Study II, and its researcher employees. And so I would again urge the authors to reconsider retrospectively collecting data on GnRHa exposure in the Nurses' Health Study II.

Respectfully submitted,

Lynne Millican

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(30) -- Ibid. p. 490. Hoag Fertility Services, Newport Beach, CA. - reporting 1% of 1988 GIFT patients were treated for endometriosis.
(31) -- Ibid. p. 494. Infertility, Gynecology & Obstetrics, Englewood, CO. - reporting 67% of 1987 GIFT, 5% of 1988 IVF, and 39% of 1988 GIFT patients were treated for endometriosis.
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