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Research Article

Hormonal contraception and the development of autoimmunity: A review of the literature

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Estrogens and progestins are known to have profound effects on the immune system and may modulate the susceptibility to autoimmune diseases. A comprehensive literature search was carried out using PubMed for any of 153 autoimmune disease terms and the terms contraception, contraceptive, or their chemical components with limits of Humans + Title or Abstract. Over 1,800 titles were returned and scanned, 352 papers retrieved and reviewed in depth and an additional 70 papers retrieved from the bibliographies. Based on this review, substantial evidence exists linking the use of combined oral contraceptives to a lower incidence of hyperthyroidism, an increase in multiple sclerosis, ulcerative colitis, Crohn's disease, Systemic Lupus Erythematosus, and interstitial cystitis. Progesterone only contraceptives are linked to progesterone dermatitis and in one large developing world concurrent cohort study are associated with increases in arthropathies and related disorders, eczema and contact dermatitis, pruritis and related conditions, alopecia, acne, and urticaria. Hormonal contraceptives modulate the immune system and may influence the susceptibility to autoimmune diseases with significant increases in risk for several autoimmune diseases.

Summary: Hormonal contraceptives (HCs), such as the "pill," Norplant, and vaginal rings, are very potent hormones that have effects on the immune system, which is made up of white blood cells and lymph nodes and normally defends the body against invading bacteria, viruses and parasites. This review looked at the association of HC use to the development of autoimmune diseases, where the immune system turns against the body and causes damage to organs. There is good evidence that HC use is associated with an increased risk of several serious autoimmune diseases such as Crohn's disease (which causes inflammation of the bowels), Lupus (which causes inflammation in many organs), and interstitial cystitis (which causes inflammation in the bladder). Several other rarer autoimmune diseases are also linked to HC use. People contemplating the use of HCs should be informed of these risks.

Keywords: Hormonal contraceptives, Oral contraceptive pills, Progesterone only contraceptives, Autoimmune disease, Autoimmunity

Introduction

Hormonal contraceptives are used by a large number of women of child-bearing potential. According to the United States Centers for Disease Control, in the National Surveys of Family Growth, oral contraceptives are the most popular form of family planning in the United States with 10.7 million women currently using oral contraceptives (Mosher and Jones 2010). While there is some use of hormonal contraceptives for medical indications, the vast majority of hormonal contraceptive use is

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by otherwise healthy individuals and is used to prevent pregnancy, not to treat a pathologic condition. This puts a large number of women at risk for the development of side effects from these potent hormonal agents. The only "benefit" of using hormonal contraceptives in this setting is to allow for sexual intercourse while avoiding pregnancy. Pregnancy can also be avoided by natural methods such as natural family planning and fertility awareness methods. Side effects from hormonal contraceptives can be immediate, such as menstrual irregularities, nausea, headache, breast tenderness, fatigue, irritability, decreased libido, increased weight, and affect labiality (Bayer HealthCare Pharmaceuticals Inc. 2012). However, side effects may be delayed such as inducing susceptibility to other diseases.

Sex steroids have several potent effects on the body. Sex steroid receptors can be found in almost every cell in the body, including those of the adaptive and innate immune systems. Sex steroids are strongly implicated in the development and modulation of the immune system (Schuurs and Verheul 1990; Mann et al. 1994). Estrogens have been demonstrated to enhance cellular proliferation and antibody secretion (Cutolo et al. 2010) while progestins clearly have immunomodulatory effects on the immune system, especially on T cells and T cell subsets (Tan, Peeva, and Zandman-Goddard 2015). Hormonal contraceptives also suppress pituitary gonadotropins, which have a number of additional immunomodulatory effects (Athreya, Rettig, and Williams 1998). Gonadotropin releasing hormone (GnRH) and its receptor are expressed in immune cell subsets and GnRH plays a role in programming the immune system (Tanriverdi et al. 2003). In addition, several autoimmune diseases have a marked sex predominance, with females much more susceptible to diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), autoimmune thyroid disease, and multiple sclerosis, while males are more susceptible to ankylosing spondylitis and reactive arthritis. Thus, while a specific mechanism linking hormonal contraceptives to autoimmune disease pathogenesis has not been elucidated, it is reasonable to speculate that the administration of hormonal contraceptives, either combined estrogen-progestin contraceptives or progestin-only contraceptives, would modulate the immune system and may affect the predisposition of hormonal-contraceptive users to autoimmune diseases.

To evaluate the hypothesis that hormonal contraceptive use affects susceptibility to autoimmune diseases, a literature search was performed to capture studies that have evaluated this question. These studies were analyzed in terms of their size and quality to provide insights into the linkage between hormonal contraceptive use and the subsequent development of autoimmune diseases.

Methods

The objective of this literature survey was to determine if hormonal contraceptives alter the susceptibility for autoimmune diseases. The search was performed in the PUBMED database, initially in 2012 and then again in October 2014, May 2015, and April 2016 for the following terms:

> Contraceptive OR contraceptives OR contraception OR levonorgestrel OR etonogestrel OR ethinyl estradiol OR estradiol valerate OR dienogest OR drospirenone OR norelgestromin

AND

> Any of the following autoimmune diseases:
>
> Addison's OR Agammaglobulinemia OR agglutinin OR Alopecia areata OR alveolitis OR Amyloidosis OR angioedema OR Antiphospholipid OR aplasia OR

aplastic anemia OR arteritis OR Autoimmune OR autoimmunity OR Balo OR Behcet's OR Cardiomyopathy OR Castleman OR Celiac OR Chagas OR cholangitis OR Churg-Strauss OR Cogans OR Congenital heart block OR connective tissue disease OR CREST OR Crohn's OR cryoglobulinemia OR Dermatomyositis OR Devic's OR Dressler's OR dysautonomia OR encephalomyelitis OR Eosinophilic OR Evans OR fasciitis OR Glomerulonephritis OR Goodpasture's OR granulomatosis OR Graves OR Guillain-Barre OR Hashimoto's OR Hemolytic OR Henoch-Schonlein OR herpetiformis OR Hypogammaglobulinemia OR Idiopathic pulmonary fibrosis OR IgA OR IgG4 OR Interstitial cystitis OR Juvenile arthritis OR Juvenile diabetes OR Kawasaki OR Lambert-Eaton OR leukoencephalitis OR Lichen planus OR Lichen sclerosus OR Ligneous conjunctivitis OR Lupus OR Lyme OR Meniere's OR Mooren's OR Mucha-Habermann OR Multiple sclerosis OR Myasthenia OR myelitis OR myocarditis OR myositis OR Narcolepsy OR nephritis OR nephropathy OR neuromyelitis OR neuropathies OR neuropathy OR Neutropenia OR nodosum OR Optic neuritis OR osteomyelitis OR Palindromic OR rheumatism OR PANDAS OR Paraneoplastic OR Paroxysmal nocturnal hemoglobinuria OR PNH OR Parsonage OR pemphigoid OR Pemphigus OR Pernicious OR planitis OR POEMS OR polyangiitis OR Polyarteritis OR polychondritis OR Polymyalgia OR Polymyositis OR polyneuropathy OR Postpericardiotomy OR Primary biliary cirrhosis OR Progesterone dermatitis OR Psoriasis OR Pyoderma gangrenosum OR Raynauds OR Reactive Arthritis OR Reflex sympathetic dystrophy OR Reiter's OR Retinocochleocerebral OR Retroperitoneal fibrosis OR Rheumatic OR Rheumatoid OR Romberg OR Sarcoidosis OR Schmidt OR Scleritis OR Scleroderma OR Systemic Sclerosis OR Sjogren's OR spondylitis OR Stiff person syndrome OR Susac's OR Sympathetic ophthalmia OR Takayasu's OR thrombocytopenic purpura OR thyroiditis OR Tolosa-Hunt OR Type 1 diabetes OR Ulcerative colitis OR uveitis OR vasculitis OR Vesiculobullous dermatosis OR Vitiligo.

Limits to the search were "Humans" and "Title/Abstract."

The initial search returned 1871 references, and titles were scanned to find relevant papers. A total of 352 papers were reviewed in depth, and an additional 70 papers were retrieved from the bibliographies of these papers. The search in October 2014 (limited to 2012–14) returned an additional 20 relevant papers (not including case reports, reviews, and other papers that did not bear on the question at hand). These papers were retrieved and reviewed, focusing on case-control and cohort studies. The search in May 2015 (limited to 2014–15) returned one additional relevant paper. The search for April 2016 (limited to 2015–16) returned an additional 5 relevant papers. Each paper was rated based on the parameters noted in the STROBE statement (von Elm et al. 2007). This included the following:

- Background and rationale provided?
- Objectives stated?
- Key elements of study design presented?
- Setting, locations, and relevant dates described?
- Eligibility criteria, and the sources and methods of selection of participants provided?
- Matching criteria and number of exposed/unexposed/controls provided?
- Diagnostic criteria, outcomes, exposures, predictors, potential confounders, and effect modifiers provided?
- Sources of data and details of methods of assessment provided?
- Any efforts to address potential sources of bias?
- Rationale for the study size provided?
- Information on how quantitative variables were handled in the analyses?
- Statistical methods described, including those that control for confounding?

- Methods used to examine subgroups and interactions described?
- Missing data addressed?
- How were lost to follow-up addressed (cohort studies)?
- How was matching of cases and controls addressed?
- Sensitivity analyses described?
- Numbers of individuals at each stage of the study provided and reasons for non-participation?
- Characteristics of study participants, information on exposures and potential confounders provided?
- Number of participants with missing data for each variable of interest provided?
- Follow-up time provided (cohort study)?
- Numbers of outcome events or summary measures over time reported (cohort)?
- Numbers in each exposure category, or summary measures of exposure reported (case-control)?
- Unadjusted estimates and confounder-adjusted estimates provided with their precision?
- Other analyses reported (i.e., sub-groups)?
- Limitations of the study discussed, including magnitude and direction of potential bias?
- Source of funding provided?

Each item was assigned a maximum score of 1, and the result converted into a percentage. Also noted for each study were the odds ratio (OR) or relative risk (RR) and the 95 percent confidence interval. Briefly, if the population under study is divided into those with and without exposure to a hormonal contraceptive, and is further divided into those who subsequently develop the disease or do not develop the disease, the relative risk is the percentage of those in the exposed group with the disease divided by the percentage of those in the unexposed group who develop the disease. The odds ratio is the proportion of those in the exposed group who did versus did not develop the disease divided by the proportion of those in the unexposed group who did versus did not develop the disease (Altman 1991; Deeks and Higgins 2010; Pagano and Gauvreau 2000; Parshall 2013). For all studies, if both unadjusted and multivariable adjusted ORs or RRs were stated, the multivariable adjusted ORs and RRs were summarized here.

Results

The initial search showed no relevant literature for a number of the less frequent autoimmune diseases. Those autoimmune diseases that had at least one case-control or cohort study that evaluated the impact of exposure to hormonal contraceptives on the subsequent development of the disease were: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn's disease, ulcerative colitis, multiple sclerosis, autoimmune thyroid disease (both hyperthyroidism and hypothyroidism), and immune skin diseases. A number of less frequent autoimmune diseases did have literature supporting a link to hormonal contraceptives, and these will be briefly mentioned in the following section. Here, each disease with supporting data will be discussed in turn, starting with those with the most studies evaluated.

Rheumatoid arthritis

Rheumatoid arthritis is a systemic inflammatory disease that affects multiple joints of the body, typically in a symmetrical fashion, often causing joint deformity and disability. The annual incidence of rheumatoid arthritis is reported to be about 40 per 100,000 (Myasoedova et al. 2010) with the disease prevalence 0.5–1 percent in the general population (Silman and Hochberg 2001). Women are affected two to three times more often than men. Patients with rheumatoid arthritis are at increased risk for mortality, with the studies showing an over twofold increase in mortality

compared with the general population (Wolfe et al. 1994; Symmons and Gabriel 2011; Erhardt et al. 1989; Kazis, Anderson, and Meenan 1990; Pincus and Callahan 1986). It is a well-known clinical fact that pregnancy typically ameliorates the signs and symptoms of rheumatoid arthritis while the disease typically flares post-partum. Breastfeeding also appears protective. Thus an effect of hormonal contraceptives, which produce many of the same hormonal effects as pregnancy, is of interest.

The literature search produced 30 primary studies of rheumatoid arthritis and 3 meta-analyses. These are summarized in Supplemental Tables 1A and 1B (all tables are shown in descending order of quality scores). The table shows data (OR and RR) for "ever use" (meaning use of a HC at any time prior to disease onset), current use (at the time of disease onset), and past use (use that stopped prior to disease onset) of hormonal contraceptives (HCs). Of these 30 studies, four (Doran et al. 2004; Vandenbroucke et al. 1982; Wingrave and Kay 1978; Hazes et al. 1989) showed a decreased risk for the development of rheumatoid arthritis with cHC use with the rest of the studies failing to show significant differences. One study (Pedersen et al. 2006) showed an increased risk for the subset of rheumatoid arthritis patients with anticitrullinated protein antibody positivity. The meta-analyses for "ever use" of cHCs showed OR that was significant in one study (Spector and Hochberg 1990) and not in another (Romieu, Hernandez-Avila, and Liang 1989) while analyses of RR failed to show significant differences. Meta-analysis of current use or past use did not show a significant reduction in risk.

On analysis of these papers a few trends become apparent. Early studies, predominately case-control studies, suggested that hormonal contraceptives exert a protective effect against the development of rheumatoid arthritis. However, the quality of these studies was poor, and some were funded by the pharmaceutical companies that sell oral contraceptives. The more recent studies, especially those published since 2000, tended to show either no decrease in risk or an increased risk. The meta-analyses were all published before 2000 and therefore did not take into account these more recent data. Interestingly cohort studies, which typically evaluate many individuals for the development of disease over time, did not show a reduced risk of rheumatoid arthritis with the exception of one early study of relatively poor quality (Wingrave and Kay 1978). Some have hypothesized that case-control studies tend to select patients with more severe disease, while the cohort studies select patients with milder disease. The suggestion was that cHCs lessens the severity of rheumatoid arthritis and so those with mild disease may have been missed in the case-control studies. In opposition to this is the data from Pedersen (Pedersen et al. 2006), which showed a significantly increased risk in a case-control study in patients positive for antibodies to citrullinated proteins (ACP), a subgroup that typically has more severe disease. Others have hypothesized that the lower estrogen doses in the third and fourth generation cHCs are less protective against the development of rheumatoid arthritis and thus the early results have not been carried forward. Another observation is that the RR and OR for studies based in the United States have rarely shown a decreased risk, while those from the European Union (EU) have often shown a decreased risk. Thus, geographic factors may be at play as well. But the overall trend is similar in the US and EU over time: both fail to show a protective effect in more recent studies (which are also of higher quality) and some analyses show an increased risk. The most recent study, from China, did not show an effect of cHCs on the risk of rheumatoid arthritis (Adab et al. 2014).

Crohn's disease

Crohn's disease is an inflammatory disease of the gastrointestinal tract. Typical symptoms include fatigue, prolonged diarrhea with abdominal pain with or without gross bleeding, weight loss, and fever (Mekhjian et al. 1979). The incidence of Crohn's disease is 3.1 to 20.2 cases per 100,000 person-years (Munkholm et al. 1992; Loftus 2004; Molodecky et al. 2012), with a prevalence estimated at 201 per 100,000 population (Kappelman et al. 2007). Crohn's disease shows an increased incidence of about 40 percent in women (Munkholm et al. 1992). The age of onset peaks between 15 and 25 years, suggesting a hormonal influence. Approximately half of Crohn's disease patients will develop strictures or penetrating disease within 10 to 20 years (Solberg et al. 2007; Thia et al. 2010). Mortality appears increased in Crohn's disease (HR 1.52, 95% CI: 1.32–1.74 in one meta-analysis; Canavan, Abrams, and Mayberry 2007) with increased mortality from infectious causes, other GI disorders, small intestinal cancer, respiratory disease, liver disease, and diseases of the urinary tract organs (Jess et al. 2002; Hutfless et al. 2007).

Overall, 17 primary studies and two meta-analyses were identified which evaluated the effect of cHCs on the later development of Crohn's disease (Supplemental Table 3). Of the 17 primary studies, 4 showed a significantly increased risk for either "ever use" (Ng et al. 2012; Sicilia et al. 2001; Katschinski 1993) or current use (Katschinski 1993; Khalili et al. 2013) or past use (Khalili et al. 2013). None of the primary studies showed a significantly decreased risk. One meta-analysis (Godet, May, and Sutherland 1995) gave a significantly increased RR of 1.44 (95% CI 1.12–1.86) for "ever use" of cHCs. A meta-analysis published in 2008 showed a significantly increased risk for current use (RR of 1.46 [1.26–1.70]) compared with 1.04 (0.816—1.340) for past use. Recent studies have produced similar findings as older studies, with the highest OR published in 2012 (9.04 [1.11–73.6]). Overall these studies indicate that use of cHCs conveys an increased risk of Crohn's disease, especially current use.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the colon (large intestine). The combination of inflammation and ulceration can cause abdominal discomfort and diarrhea. In North America, incidence rates range from 2.2 to 19.2 cases per 100,000 person-years (Loftus 2004; Molodecky et al. 2012), while the prevalence in adults in the United States in one large study was estimated as 238 per 100,000 population (Kappelman et al. 2007). Ulcerative colitis is relatively equally distributed between men and women, with perhaps a slight increase in males (Loftus 2004). The age of onset peaks between 15 and 30 years and again from 50 to 70, suggesting a hormonal influence. Approximately 20 percent of patients with UC will eventually require a colectomy (Solberg et al. 2009; Höie et al. 2007; Langholz et al. 1992; Allison et al. 2008). Mortality is slightly increased in ulcerative colitis (HR 1.2, 95% CI 1.22–1.28) with increased mortality from infectious causes, other GI disorders and colorectal cancer (Jess et al. 2007; Jess et al. 2013; Bewtra et al. 2013).

Overall 14 primary studies and one meta-analysis were identified that evaluated the effect of cHCs on the later development of ulcerative colitis (Supplemental Table 4). None of the primary studies has shown a statistically significant decrease in risk, while two showed a significant increase in risk for the development of ulcerative colitis with "ever use" of cHCs (Boyko et al. 1994; Parrello et al. 1997). One meta-analysis examined "ever use" and failed to show a

significant difference (Godet, May, and Sutherland 1995), while another meta-analysis examined current use and found a significantly increased relative risk of 1.28 (1.06–1.54). Overall these studies suggest that use of cHCs conveys an increased risk of ulcerative colitis, especially current use.

Systemic lupus erythematosus

Systemic lupus erythematosus is a systemic autoimmune disease affecting multiple organ systems. More than 90 percent of cases of systemic lupus erythematosus occur in women, frequently starting at childbearing age. The annual incidence of systemic lupus erythematosus estimated by the Centers for Disease Control ranges between 1.8 and 7.6 per 100,000 persons per year in the continental United States (Uramoto et al. 1999; Rus, Hajeer, and Hochberg 2001). The reported prevalence ranges from 52 cases per 100,000 population (Helmick et al. 2008) to estimates as high as 1 in 1000 (Lawrence et al. 2008). Mortality is clearly increased in SLE with mortality rates ranging from two to five times higher than that of the general population (Borchers et al. 2004; Yurkovich et al. 2014). Crude death rates are increased with age, among women (five times higher than in men), among blacks (three times higher than in whites) (Sacks et al. 2002) with increased mortality in Asia and Africa compared with the United States (Kasitanon, Magder, and Petri 2006; Trager and Ward 2001; Murali et al. 1997; Wang et al. 1997).

Systemic lupus erythematosus has been observed by some (Petri, Howard, and Repke 1991; Ruiz-Irastorza et al. 1996), but not others (Lockshin et al. 1984; Lockshin 1989; Meehan and Dorsey 1987; Urowitz et al. 1993), to be exacerbated by pregnancy. Similarly, several studies have suggested that cHCs may induce flares of systemic lupus erythematosus disease activity (Jungers et al. 1982; Julkunen 1991; Julkunen, Kaaja, and Friman 1993; Petri and Robinson 1997), while others do not suggest an increased risk (Sánchez-Guerrero et al. 2005; Petri et al. 2005). It is, however, generally agreed that cHCs increase the risk of thrombosis particularly in the subset of systemic lupus erythematosus patients with concomitant antiphosphiolipid antibody syndrome (a disorder that predisposes individuals to clotting) (ACOG Committee 2006; Urbanus et al. 2009).

Seven studies published evaluated the effect of hormonal contraceptives on susceptibility to systemic lupus erythematosus (Supplemental Table 5). A significantly increased risk for development of systemic lupus erythematosus with use of cHCs was shown for "ever use" in two studies (Costenbader et al. 2007; Sanchez-Guerrero et al. 1997), for current use in one study (Bernier et al. 2009) and for past use in one study (Costenbader et al. 2007). None of the studies showed a decreased risk. While no meta-analyses of these studies have been performed, the uniformity of the results implicate cHCs as an important risk factor for the subsequent development of systemic lupus erythematosus.

Multiple sclerosis

Multiple sclerosis is an autoimmune inflammatory disease of the central nervous system with resultant nerve damage causing sensory loss (numbness, tingling), spasticity, loss of bowel or bladder control, sexual dysfunction, imbalance walking, difficulty speaking, tremor, visual disturbances, muscle twitching and weakness, fatigue, dizziness, and difficulties with attention span, concentration, memory, and judgment (Katz Sand and Lublin 2011; Polman et al. 2011) with worsening disability over time (Chruzander et al. 2013). The mean age of multiple sclerosis onset ranges from 28 to 31 years (Goodin 2014). Women are afflicted with multiple sclerosis 1.4 to 2.3 times more frequently

than men (Alonso and Hernán 2008), and the incidence in women appears to be increasing (Koch-Henriksen and Sørensen 2010). Depending on the region and population evaluated (male vs. female) the incidence of multiple sclerosis has been estimated at 1.12 to 11.52 per 100,000 person-years (Alcalde-Cabero et al. 2013; Mackenzie et al. 2014; Niedziela, Adamczyk-Sowa, and Pierzchała 2014). The prevalence of multiple sclerosis varies geographically, but is estimated at 100–135 per 100,000 in the United States and 60 per 100,000 in Europe (Hernán, Olek, and Ascherio 1999; Ebers 2008; Koch-Henriksen and Sørensen 2010; Simpson et al. 2011; Niedziela, Adamczyk-Sowa, and Pierzchała 2014). Patients with multiple sclerosis have an increased risk of mortality of about 2.5 (Kingwell et al. 2012; Manouchehrinia et al. 2014).

Six studies (3 cohort studies and 3 case-control studies) were identified that evaluated the impact of cHCs on the subsequent development of multiple sclerosis (Supplemental Table 6). Two studies showed a significantly increased risk for the development of multiple sclerosis with "ever use" of cHCs (Hellwig et al. 2016; Kotzamani et al. 2012) with a similarly increase risk noted in one study for current use or past use (Hellwig et al. 2016). Overall these studies suggest that use of cHCs may convey an increased risk for the subsequent development of multiple sclerosis.

Thyroid disease

Hyperthyroidism and hypothyroidism are both linked in many cases to autoimmune mechanisms. The most common manifestations of autoimmune hyperthyroidism (Grave's disease) include weight loss, tachycardia, increased appetite, nervousness, irritability, tremor and sweating, as well as goiter (thyroid enlargement), eye disease, and occasionally a skin disease referred to as pretibial or localized myxedema (Bartalena 2013). Hyperthyroidism is more common in women by a 5:1 ratio with a prevalence estimated as 1.3 percent (Hollowell et al. 2013), and the 12-year incidence was 4.6 per 1000 women (Holm et al. 2005). Graves' disease treated in a hospital setting has been associated with higher mortality with a hazard ratio of 1.42 (95% CI 1.25–1.60) (Donangelo and Braunstein 2011).

Three studies (one cohort and two case-control studies) were identified which evaluated the impact of cHCs of the subsequent development of hyperthyroidism (Supplemental Table 7). The two case control studies looked at "ever use" of cHCs and showed a significant decrease in the risk for the subsequent development of hyperthyroidism. In one study with relatively few cases this was estimated at an RR of 0.168, although this study was hampered in that it did not separate out hormone replacement therapy and use of cHCs. In the other study, which focused on use of cHCs, the OR was 0.68. The cohort study evaluated current use and past use but did not report statistical significance. Overall these studies suggest that use of cHCs may be protective against the subsequent development of hyperthyroidism, although the small number of studies and their quality makes it difficult to develop a firm conclusion.

The most common cause of hypothyroidism (in iodine-sufficient areas of the world) is chronic autoimmune (Hashimoto's) thyroiditis (Weetman and McGregor 1994). Hypothyroidism is five to eight times more common in women than men (Aoki et al. 2007). The prevalence of clinical hypothyroidism varies from 0.1 to 2 percent with an incidence in women estimated at 0.8/1000 survivors/year (95% CI 0.5–1.4) (Vanderpump et al. 1995; Vanderpump and Tunbridge 2000; Canaris et al. 2000; Hollowell et al. 2002; Aoki et al. 2007). The evidence for an impact of hypothyroidism on mortality is conflicting (Thvilum et al. 2012), although the most recent cohort study

suggests an increased risk similar to that for hyperthyroidism (hazard ratio 1.52; 95% CI 1.41–1.65) (Thvilum et al. 2013).

The same three studies that evaluated the effect of cHCs on the development of hyperthyroidism also looked at hypothyroidism (Supplemental Table 7). These studies show no evidence of any statistically significant effect of cHCs on the subsequent development of hypothyroidism. Current use was only evaluated in one study, and no effect was seen. Overall these studies do not suggest that use of cHCs conveys an increased or decreased risk on the subsequent development of hypothyroidism.

Skin diseases

Five studies were identified which evaluated the effect of cHCs on various dermatologic conditions, including some with clear immune mediated mechanisms (Supplemental Table 8). Significant increases were seen for the effect on cHCs on the subsequent development of eczema (current use) and pemphigus and, in one of two studies, vulval lichen sclerosis. There was no significant impact noted on the development of scleroderma or psoriasis. Notable for vulval lichen sclerosis, for the paper by Günthert et al. (2008), the OR provided is for oral contraceptives (OCs) with anti-androgenic activity. The OR for all OCs was infinity.

Progesterone-only contraceptives

One large cohort study in the developing world evaluated the risk of developing a number of diseases following the use of Norplant contraceptive implants (Supplemental Table 9). This was a concurrent cohort study of women initiating use of Norplant implants compared with women initiating use of IUDs (nonhormonal) and sterilization in 8 developing countries. Women 20–40 years old were followed up six weeks after the initial visit and then biannually. The study was designed to have 80 percent power to detect a doubling of event rates among implant users from a baseline incidence of 1 per 1,000 women. The study recruited 16,021 women, of whom 7977 used Norplant, 6625 IUDs and 1419 sterilization (International Collaborative 2001). The study based diagnosis on the ICD9 codes, and their methodology lumped several diseases together. They found significantly increased risks for the subsequent development of "rheumatism excluding the back" and for "arthropathies and related disorders" from the use of Norplant. These diagnostic categories for "rheumatism excluding the back" include diseases such as polymyalgia rheumatica; peripheral enthesopathies and allied syndromes; other disorders of the synovium, tendons and bursae; disorders of muscles, ligaments, and fasciae; and other disorders of soft tissues. For "arthropathies and related disorders," this includes diffuse diseases of connective tissue, arthropathy associated with infections, crystal arthropathies, rheumatoid arthritis and other inflammatory polyarthropathies, osteoarthrosis and allied disorders, and several others. Although it is beyond the scope of this article to review each of these conditions in depth, it should be noted that all of them carry significant morbidity, and many increase mortality in the affected individuals.

In terms of dermatological conditions, the authors found significantly increased risks for eczema and contact dermatitis, pruritis and related conditions, alopecia, acne, and urticaria. This was supplemented by one study that specifically evaluated the effect of progesterone-only contraceptives on the subsequent development of vulval lichen sclerosis. This showed a decrease risk with the use of progesterone-only contraceptives.

Other immune disorders (nondermatologic)

Several other immune-related disorders have been studied. These include interstitial cystitis (Konkle et al. 2012) where a case-control study showed significantly higher use of birth control pills in cases versus controls: 88 percent versus 82 percent; P = 0.019 (Warren et al. 2011). Another case-control study showed that use of OCs markedly increased the risk of the disease whether past (OR 4.6, 95% CI 1.74–12.1) or current use (OR 6.9, 95% CI 2.1–22.1). Interstitial cystitis was associated with vulvodynia and sexual dysfunction in a high number of cases (Gardella et al. 2011). Another study showed that use of OCs in patients with interstitial cystitis was associated with a decrease in quality of life (El Khoudary et al. 2009).

Primary sclerosing cholangitis was the subject of one case-control study using a Norwegian PSC patient registry (Andersen et al. 2014). This reported that a lower proportion of female subjects with PSC reporting "ever use" of cHCs compared with control subjects (51% vs. 85%; P = 0.01), but also reported lower use of non-hormonal contraception in primary sclerosing cholangitis patients compared with controls (27% vs. 48%, P = 0.009). They also noted a strong linear relationship between parity and age at primary sclerosing cholangitis diagnosis suggesting that pregnancy may delay primary sclerosing cholangitis onset. In contrast, a recent, relatively small study in Iran of patients with ulcerative colitis found that oral contraceptives increased the risk of the development of sclerosing cholangitis, but there were relatively few women who developed this complication (Khosravi Khorashad et al. 2015).

Primary biliary cirrhosis (Gao, Qiao, and Wang 2015; Feld and Heathcote 2003) was the subject of a case-control study which showed that OC use was reported by fewer primary biliary cirrhosis patients compared with controls (RR of 0.6, 95% CI of 0.5–0.8) (Corpechot et al. 2010). The authors note that due to the small number of cases and relatively low level of statistical significance these results should be interpreted with caution.

Antiphospholipid antibody syndrome is a prothrombotic autoimmune disease (Lackner et al. 2016). One recent study evaluated 1,190 women who were referred to an infertility clinic. They found that hormonal contraceptives correlated with an increased risk to develop antiphospholipid antibodies, and the risk increased for increasing duration of use (Ulcova-Gallova et al. 2015). The authors did not look at the occurrence of the clinical antiphospholipid antibody syndrome. They suggest prolonged use of hormonal contraceptives may affect female autoimmunity through the induction of autoantibodies.

One case-control study of complex regional pain syndrome showed no effect of the use of cHCs (OR 1.0, 95% CI 0.5–1.9) (de Mos et al. 2009). Aplastic anemia, in one population-based case-control study in Thailand, was found not to be associated with the use of OCs with a multivariate RR of 0.6 (0.2–1.7) (Issaragrisil et al. 1997). A cohort study of black women in the United States did not show an effect of OCs on the development of sarcoidosis with an RR of 0.98 (95% CI 0.78–1.23) (Cozier et al. 2012).

In one uncontrolled case-series, condylar resorption of the jaw was associated with the use of OCs (Gunson et al. 2009).

Other immune disorders (dermatologic)

Hereditary angioedema is a very rare and potentially life-threatening genetic condition (Dreskin 2012). The development of hereditary angioedema and exacerbations of hereditary angioedema have been linked to estrogen use, including cHCs, and withdrawal has been shown to lead to improvement in symptoms in multiple studies (listing only

references since 2000: Bork et al. 2000; Andre 2003; Bork, Fischer, and Dewald 2003; Bouillet et al. 2003; André et al. 2003; Visy et al. 2004; Bouillet et al. 2008; Bork et al. 2009; Caballero et al. 2012; Bork et al. 2013; Miranda et al. 2013). On the other hand, progesterone-only contraceptives have been linked to improvement in hereditary angioedema (Bouillet et al. 2008; Saule et al. 2013).

Erythema nodosum has been linked to the use of cHCs in several small studies (Hannuksela 1973; Fernandes, Maceira, and Muniz 1994; Psychos 2000; Malaviya et al. 1999).

Autoimmune progesterone dermatitis is a very rare condition which has been linked to the luteal phase of a woman's menstrual cycle, and may be triggered or worsened by progesterone-only contraceptives and in some cases aided by use of cHCs (Hart 1977; Maguire 2009; George and Badawy 2012; Fournier 2015).

Hidradenitis suppurativa was temporally linked to use of cHCs in a small study of seven women (Stellon and Wakeling 1989).

Discussion

Hormonal contraceptives are unique among prescription medications in that they do not treat a pathologic condition nor seek to enhance the normal function of a body system or organ, but rather serve to impair the normal function of a body system: the reproductive system. The mechanism by which HCs exert their effects is by use of potent analogs of sex steroids, which have profound effects on a number of physiological processes, including the immune system. Not surprisingly, there are consequences to the widespread use of hormonal contraceptives, some of which are immediate or short term, and others of which take longer to develop. In this paper the effect of these agents on the development of autoimmune disease was surveyed. Based on this analysis, the level of evidence for an association, or lack of association, with various immune diseases can be summarized. This information is largely captured in the aforementioned tables. Based on these analyses, the following statements appear supported by the data available.

Rheumatoid arthritis (RA) is the most thoroughly studied autoimmune disease with a total of 29 primary publications reviewed which evaluated the effect of prior use of cHCs (Supplemental Table 1) as well as three meta-analyses (Supplemental Table 2). Rheumatoid arthritis is known to be affected profoundly by hormonal factors, both in that it is most prevalent among women and that it frequently goes into remission during pregnancy. As use of cHCs produces a state resembling pregnancy, it is reasonable to postulate that use of cHCs may decrease the risk of the development of rheumatoid arthritis. While the earlier studies suggested that cHCs may lower the risk of rheumatoid arthritis, more recent studies show no decrease in risk with some suggesting an increased risk of rheumatoid arthritis with use of cHCs. In fact, one recent study suggested on multivariate analysis that "ever use" of OCs was associated with an increased risk of a subset of rheumatoid arthritis characterized by antibodies to citrullinated proteins (Pedersen et al. 2006). In addition, studies have been performed evaluating whether the use of cHCs impacts on the clinical course of rheumatoid arthritis, and these have not shown the marked positive effects typically seen with pregnancy (Bijlsma, Huber-Bruning, and Thijssen 1987; Camacho et al. 2011). Based on the totality of the data reviewed, it does not appear that use of cHCs has a protective effect on the development of rheumatoid arthritis, nor can it be definitively stated that it increases the risk for rheumatoid arthritis.

The inflammatory bowel diseases Crohn's disease (Supplemental Table 3) and ulcerative

colitis (Supplemental Table 4) have been the subjects of 13 and 20 primary studies, respectively, and several meta-analyses. For Crohn's disease, both published meta-analyses indicate an increased risk in the development of Crohn's disease for current use or "ever use" of cHCs with no effect for past use. The most recent studies support this association. The most recent meta-analyses of ulcerative colitis indicate a slight increased risk in the development of ulcerative colitis for current use of cHCs with no effect of past use. Recent data also suggests that in women with established Crohn's disease, long-term use of cHCs is associated with an increased risk of surgery (Khalili et al. 2016). Overall the data indicate that the use of cHCs significantly increases the risk of developing Crohn's disease and slightly increases the risk of developing ulcerative colitis.

Systemic lupus erythematosus (SLE) has been the subject of seven studies, and these generally indicate that the use of cHCs increases the risk of SLE (Supplemental Table 5). Of the five studies that looked at "ever use" of cHCs, three showed a statistically significant increased risk of development of systemic lupus erythematosus while the other two showed no effect. Both current use and past use has been associated with the development of systemic lupus erythematosus in the highest quality cohort studies. Overall the data indicate that the use of cHCs increases the risk of systemic lupus erythematosus.

Multiple sclerosis has been the subject of six studies (Supplemental Table 6). Of these five looked at "ever use" of cHCs, and two showed a statistically significant increase in the risk of developing MS. The other three did not disclose a statistically significant increase or decrease in risk. It is noteworthy that the most recent studies showed this increased risk, and these were of high quality. Overall the data suggest that the use of cHCs may increase the risk of developing MS.

Thyroid disease (Supplemental Table 7) has been the subject of three studies. These studies are of variable quality, but both studies that looked at "ever use" of cHCs indicate a decreased risk of the development of hyperthyroidism and no effect on the development of hypothyroidism. The low number of studies, coupled with the low number of patients with hyperthyroidism in one of the studies, makes these conclusions uncertain. However, it appears unlikely that use of cHCs increases the risk for the development of thyroid disease.

A number of skin diseases have been evaluated in five studies (Supplemental Table 8). Although each skin disease was evaluated in a single study, with the exception of vulval lichen sclerosis, these suggest there may be an increase in the incidence of eczema, psoriasis, pemphigus, and vulval lichen sclerosis with use of cHCs. Additional study is needed to confirm these preliminary findings.

Use of progesterone-only contraceptives was evaluated in one large cohort study (Supplemental Table 9; International Collaborative 2001). This study indicates that use of progesterone-only contraceptives is associated with increased risk for the development of rheumatism, arthropathies (including rheumatoid arthritis), eczema and contact dermatitis, pruritis and related conditions, alopecia, acne, and urticaria. Again, additional study is needed to confirm these intriguing findings.

In addition, there are two studies published on the effect of the use of cHCs on the development of interstitial cystitis. Both indicate an increased risk for the development of interstitial cystitis with cHC use. One study suggests a decreased risk, and one an increased risk of the rare autoimmune disease sclerosing cholangitis. Single studies suggest a decreased risk for primary biliary cirrhosis, while no effect was seen on complex region pain syndrome, aplastic anemia, and sarcoidosis. Smaller case series support a link

between cHC use and the development of hereditary angioedema, erythema nodosum, hidradenitis suppurativa, and autoimmune progesterone dermatitis (the latter linked to the use of progesterone-only contraceptives).

It is interesting to note that the prescribing information for cHCs typically does not mention any of these findings. The prescribing information for YAZ notes that there have been post-marketing cases of SLE, angioedema, erythema nodosum, and erythema multiforme, among others. They note that "Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure" (Bayer HealthCare Pharmaceuticals Inc. 2012, 12). The prescribing information for Apri (desogestrel and ethinyl estradiol) does not mention autoimmune diseases (Barr Laboratories Inc. 2016). However, it does list several "noncontraceptive benefits" that were "supported by epidemiological studies."

Similarly the prescribing information for Jadelle (levonogestrel implants) notes, "In some rare cases autoimmune diseases such as scleroderma, LED (lupus erythematosus disseminata), or rheumatoid arthritis have been reported in users of levonorgestrel implants. No causal relationship to implants containing levonorgestrel has been established" (Bayer New Zealand Limited 2010, 5). The Norplant II prescribing information does note rare reports of various autoimmune diseases in Norplant implant users. However, they go on to state, "While it is believed that the occurrence of autoimmune diseases among NORPLANT implant users is coincidental, health-care providers should be alert to the earliest manifestations of autoimmune disease in users of Jadelle implants" (Population Council n.d., 16–17).

The literature supports a substantial risk inherent in the use of potent hormonal agents, including cHCs and progesterone-only contraceptives, to predispose users to subsequent development of autoimmune diseases. These risks currently are not acknowledged in prescribing information and the information conveyed to women before they receive these agents. It would be of great benefit to patients if the Food and Drug Administration evaluated this information and made certain it was appropriately conveyed to the public. Additionally, it can be argued that the obligation of informed consent compels physicians to discuss these risks with their patients and apprise them of alternative methods to avoid pregnancy that do not increase the risks of autoimmune diseases.

Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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