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Metabolic effects of implantable steroid contraceptives for women

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Abstract

The metabolic impact of progestin-only contraceptives is less than that of combined oral contraceptives. Subdermal contraceptive implant systems that provide a sustained release of low levels of progestins are now becoming widely available. This review evaluates the metabolic effects of currently available products that release the progestins levonorgestrel (Norplant, Jadelle, and their Chinese equivalents); etonogestrel (Implanon); nomegestrol acetate (Uniplant); and Nestorone, formally called ST-1435 (Nestorone implant/Elcometrine). Data on liver, kidney, and renal function; carbohydrates and insulin release; hemostasis; blood pressure; and lipids are considered.

The metabolic effects reported for these methods as a whole were minimal. Any changes were generally within the normal range for the populations studied and, therefore, are unlikely to be of clinical significance. However, all published studies have been conducted in healthy populations of women. To inform clinical practice, the field would be well served to have additional empiric data from well-designed, well-implemented, and well-reported trials in women who are deemed to be at elevated risk for certain diseases including cardiovascular disease and diabetes.

Keywords: Metabolism; Implants; Norplant; Jadelle; Implanon; Uniplant; Surplant; Elcometrine; Nestorone; Sino-Implant; Levonorgestrel; Etonogestrel; Nomegestrol acetate; ST-1435

1. Introduction

Certain hormonal contraceptives, in particular combined oral contraceptives, are well known to affect the metabolic system and induce changes in lipids, lipoproteins, carbohydrate metabolism, and in certain hemostatic factors. The metabolic impact of progestin-only contraceptives is less well studied. However, progestin-only pills and progestin-only injectables do not have the same magnitude of effect on metabolic indicators as do combined oral contraceptives [1]. Subdermal contraceptive implant systems that provide a sustained release of low levels of progestins have been under development for over 20 years. The Norplant system (levonorgestrel capsules manufactured by Leiras Oy, Turku, Finland), which releases low levels of levonorgestrel, is the most widely available of the progestin implants. Newer, second generation systems, such as Implanon (etonogestrel single implant, NV Organon, Oss, The Netherlands) and Jadelle (levonorgestrel rods, Leiras Oy, Turku, Finland), have only recently become available.

This review focuses on the metabolic effects of currently available contraceptive implant products. The effects of steroids in dosages other than those provided by these implant systems (for example, oral pills) are not covered in this paper. Data on liver, kidney, and renal function; carbohydrates and insulin release; hemostasis; blood pressure; and lipids will be reviewed. A summary of the potential clinical relevance of any significant findings is presented.

2. Methodology

Multiple, complementary sources were used to identify papers for this review. A comprehensive list of publications related to Norplant and Jadelle levonorgestrel implants (n = 467) and Nestorone implants (n = 51) was kindly provided by Dr. Harold Nash of the Population Council. All publications specifically related to metabolism were reviewed and included in this summary. Several articles published in Chinese journals with data on the metabolic effects of Chinese levonorgestrel contraceptive implants (Implant No. 1 and No. 2, also called Sino-implant or Sinoplant) were kindly provided by Dr. Han Li-Hui. In addition, by using Medline, the literature was searched for all implant types

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and metabolic changes using the following search strategy: (circulatory and respiratory physiology OR lipids OR insulin OR hyperinsulinemia OR metabolism) AND (drug implants OR implant OR rod OR rods OR norplant OR jadelle OR implanon OR surplant OR elcometrine OR uniplant OR ST-1435) AND (levonorgestrel OR norgestrel OR Norplant OR Jadelle OR Implanon OR Surplant OR Elcometrine OR Uniplant OR 3-keto-desogestrel OR ST-1435 OR nomegestrol OR etonogestrel OR nestorone)) AND human. Two hundred seventy-three articles were identified. Finally, a Popline search was conducted with specific attention to Implanon, Etonogestrel, Surplant, Uniplant, nomegestrol acetate, and Sinoplant. Fifty-one articles were identified. After overlap of the different search strategies was eliminated, a total of 75 articles published through April 2001 were included in this review.

Throughout this review, priority is given to data from randomized, controlled clinical trials and then to well-designed, controlled trials without randomization and then to well-designed cohort studies. In many cases, the presentation of methods and results was incomplete, which made interpretation of the data difficult. Where relevant, this is noted.

3. Norplant levonorgestrel implants

Norplant implants consist of six flexible Silastic capsules, each 34 mm in length and 2.4 mm in diameter, containing 36 mg of levonorgestrel for a total of 216 mg levonorgestrel. The initial release rate of levonorgestrel is approximately 85 μg/day, dropping to approximately 50 μg/day by 9 months, to about 35 μg/day by 18 months, and then to about 30 μg/day during years 3 to 5 [2]. The method is designed to provide contraceptive protection for 5 years; however, new evidence indicates that the system may be highly effective in many women for 7 years or longer [3,4]. Given the release profile for levonorgestrel, hormone-induced changes in certain metabolic parameters should be greatest during the first year of use and least in the latter years of use. Following removal of Norplant, levonorgestrel rapidly clears from the plasma [5].

The Chinese No. 1 implant system (Yalujiang Pharmaceutical Factory, People's Republic of China) is also a six Silastic capsule system that contains a total of 216 mg levonorgestrel. It was designed to be identical to the Norplant system. Information from the single paper found with data on the metabolic effects of implant No. 1 is included in this section.

3.1. Lipid effects

Eighteen publications were found reporting the evaluation of lipid changes during and following use of Norplant implants. These publications include information from 13 studies and from sites in 10 countries. Five of these publications included sequential data on the same population of users followed over increasing periods of time [6–10]. The longest period of follow-up was 5 years. Only four studies were longitudinal trials that included a nonhormonal control group [11–14]. The largest study (a total of 351 participants), funded by World Heath Organization (WHO), was the only multicenter trial [11]. Two studies were cross-sectional [15,16]. All but one [17] evaluated changes in the fasting state.

Laboratory methodologies were not well presented in many of the papers. Most, although not all, investigators used quality control serum samples purchased from commercial vendors to monitor lipid determinations. Laboratories in several studies participated in an external lipid quality assurance program supported by the WHO that included sending samples to a laboratory in the UK [6–12]. Two papers did not clearly specify their assay methodology [14, 18].

Total cholesterol levels generally decreased significantly during Norplant use [6–15,19–23]. In the longitudinal study with the longest follow-up (5 years), total cholesterol levels decreased to a greater extent during the earlier follow-up periods and tended to return toward baseline in years 4 and 5, which is consistent with the known decrease in release rate of levonorgestrel over time [9,10]. Total cholesterol was reported to increase in only one study, which was cross-sectional, and then only at some time points (6 months to 5 years), with no apparent pattern [16]. One study found no significant change in total cholesterol [17]. However, this was the only study that evaluated lipid profiles in nonfasting participants. Finally, in the one study that reported lipid levels following Norplant removal, total cholesterol remained significantly below baseline levels 6 months post-removal [10]. Given the rapid clearance of levonorgestrel after Norplant removal, this observation is difficult to explain physiologically. The absence of a nonhormonal control group further complicates interpretation. Overall, Norplant appears to cause a slight decrease in total cholesterol.

The majority of studies that together included sites in eight countries reported significant decreases in triglycerides over follow-up periods of up to 5 years [6,12,15,19,21]. Only one study (from Indonesia) reported an increase in triglycerides, which was at just one of four follow-up time periods, with the other three follow-up periods showing nonsignificant decreases compared with baseline [14]. Four publications, including two from Indonesia, reported no significant changes in triglycerides [13,16,17,20]. Of these four studies, one studies was cross-sectional [16], and another used nonfasting serum samples [17]. The lack of effect on triglyceride levels in the longitudinal study from Indonesia may reflect population or ethnic differences. The Indonesian center in the WHO multicenter study reported the smallest changes in triglycerides [11]. Triglycerides returned to baseline in the single longitudinal study that reported levels after removal [10]. Overall, Norplant appears to cause a decrease in total triglycerides. Moreover, the

decreases in triglycerides (on a percent basis) compared with baseline were consistently greater than those reported for total cholesterol.

Reports of LDL changes during Norplant use are more variable than those for either total cholesterol or triglycerides. These differences may reflect the fact that most investigators derived LDL levels through calculation that included three other lipids rather than measure it by direct determination. A number of studies reported decreases in LDL [6,7,11–15,21]; however, those studies that included an intrauterine device (IUD) control group reported decreases that were only occasionally significantly different than the control [11–14]. Two studies reported no changes in LDL during the first 1 to 2 years of use [17,20]. In the two studies that showed any increases in LDL, the increases were limited to a single time point (6 months) [16,19]. Overall, LDL cholesterol levels do not change or slightly decrease in Norplant users.

Like those of LDL, reports of changes in HDL during Norplant use are variable. Several studies reported significant decreases in HDL [11,12,19,20]. Three groups reported no change in HDL over time [13,15,17]. Another group reported no change in the first 9 months, but a slight and significant increase in month 12 [21]. Yet another group reported a significant increase compared to a control IUD group 6 months after insertion, but nonsignificant decreases in months 12 to 24 [14]. Finally, in a 5-year follow-up study in Singapore, HDL changes varied over time. Significant increases were seen at 12 months after insertion and 6 months following removal, whereas significant decreases were seen at 3 and 4 years, with levels identical to baseline at 2 and 5 years [10].

The variable and inconsistent results across studies reporting HDL may reflect population, dietary, or ethnic differences or different methodologies for measuring HDL [24]. Of the longitudinal trials that included an IUD control group, two reported decreases in HDL [11,12], and two studies from Indonesia reported no change [13,14]. Of note, the Indonesian center in the multicenter WHO trial was the only center that did not report a decrease in HDL. This would support a hypothesis that population, and possibly dietary, differences influence HDL response. Overall, Norplant appears to cause a slight decrease or no change in HDL levels.

A limited number of studies have evaluated apolipoproteins [11–13,18]. In all studies, apolipoprotein AI decreased during the first 12 months. In three of the four studies, the decreases were also seen during the second year [11–13]. The changes paralleled HDL changes in two of the three studies reporting both values [11,12]. Apolipoprotein AII showed no change in two studies [11,13], and in two studies only slight decreases that were not significant at all time points were reported [12,18]. Apolipoprotein B tended to decrease slightly, but these differences were not significant [11–12,18]. In the three studies that also reported LDL levels, the results paralleled the observations for LDL [11–13]. Overall, mean apolipoprotein AI levels appear to decrease in Norplant users, whereas apolipoprotein AII and B levels do not change.

Some studies reported ratios of HDL to total cholesterol, LDL to total cholesterol, HDL to LDL, apolipoprotein AI/AII and apolipoprotein AI/B. The changes were inconsistent across studies. The HDL to cholesterol ratio was seen to increase, decrease, and not change. In one study, there was no change in the HDL to cholesterol ratio when compared with the baseline ratio; however, the values for Norplant users were significantly lower than the IUD control group, as the ratio for the IUD group appeared to increase slightly over time [11]. Another study reported slight decreases in HDL to cholesterol ratio; however, the values were significantly different than the IUD control group only at later time points (approximately 18 and 24 months), which is contrary to what would be expected based on levonorgestrel release rates [12]. In the one study with follow-up over 5 years and after removal, the HDL to cholesterol ratio increased in the first year, was the same as baseline in year 2, decreased compared to baseline in years 3, 4, and 5, and was the same as baseline 6 months after removal [10]. Several other investigators reported slight increases in the HDL to cholesterol ratio during the first year [13,14,21]. Overall, defining and interpreting any changes in the HDL to cholesterol ratio with Norplant use is challenging. In contrast, the LDL to total cholesterol ratio was reported in only two publications and did not change significantly from baseline in either study [11,12].

With regard to HDL/LDL ratios, one study reported no change during the first 2 years of use compared with baseline, but a significant decrease when compared with an IUD control group [11]. In a second study, mean HDL/LDL ratios appeared to be lower than those of the IUD control group at each time point over 3 years; however, statistical testing was not presented [13]. A third study reported slight decreases during the first 2 years of use that were significantly different than baseline at three time points, and significantly different than the IUD comparison group at three time points [12]. Two of the three time points overlapped. In the one long-term follow-up study, which did not have a control group, significant increases were reported at all but the 4-year time point, when a significant decrease was reported. [9]. In that study, the HDL/LDL ratio was significantly elevated 6 months following removal when compared to baseline [10]. Overall, considering the most relevant studies to be the longitudinal trials with a nonhormonal control group, HDL/LDL ratio appears to decrease slightly in Norplant users.

Significant decreases in apolipoprotein AI/AII and AI/B ratios were reported in two studies [11,12]. A third study reported slight decreases in the AI/B ratio over a 2-year follow-up period, but statistical testing of the changes was not presented [18]. No change in apolipoprotein AI/B was reported in a fourth study [13].

In summary, lipids and lipoproteins have been evaluated

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extensively over the past decades in the context of establishing links between levels of these parameters and risk for cardiovascular disease. The consistent decreases in mean total cholesterol and triglycerides reported in populations of Norplant users are in the direction of lowering overall cardiovascular risk [24,25]. Data on mean values for HDL/total cholesterol, apolipoprotein AI/AII, and AI/B ratios are limited, but in the direction of an increased cardiovascular risk [25,26]. In all studies of Norplant that reported a significant decrease in HDL or the HDL to cholesterol ratio, the percent decrease in mean triglyceride levels in the study population exceeded the decreases in either of these values. For example, in the rigorous WHO multicenter study, the decline in triglycerides (in the range of 15–20%) was substantially greater than those for total cholesterol, for HDL and apolipoprotein AI (all around 10%), and for the ratio of HDL to cholesterol, which decreased even less. Fasting plasma triglyceride level is an independent risk factor for coronary heart disease (CHD) in women, and two recent studies found that the risk of arterial disease fell when plasma triglycerides levels were reduced [reviewed by Crook and Godsland 24]. Furthermore, the elevated risk associated with decreases in HDL-cholesterol levels appears to be graded and continuous, without clear threshold values. For example, considerable overlap exists between HDL-cholesterol distributions in individuals with and without CHD [27]. Moreover, diet and dietary composition are known to dramatically affect lipid levels and ratios. Therefore, the lipid changes summarized above, on balance, would probably not substantially modify the risk of cardiovascular disease in healthy Norplant users. One should be cautious, however, in generalizing the data from the healthy populations studied to populations with pre-existing cardiovascular disease, or even to populations that could be categorized at elevated risk. No data are available for higher risk women. To the extent that further studies could be ethically conducted, it would be valuable to gather information on the effect of Norplant on lipid profiles in women thought to be at elevated risk of cardiovascular disease.

3.2. Carbohydrate metabolism

A number of groups have investigated the effect of Norplant on carbohydrate metabolism by using various techniques, including the oral glucose tolerance test (OGTT), insulin tolerance test (ITT) and the hyperglycemic hyperinsulinemic clamp. Croxatto et al. reported in a cross-sectional study that mean fasting serum glucose levels were slightly, but significantly, elevated in Norplant users compared with IUD controls; however, no individual values were outside the normal range in these participants. OGTT were not performed [15]. Sagay et al. conducted OGTT in 21 Nigerian women 3, 6, and 12 months after Norplant insertion using an oral glucose load of 75 g [28]. Fasting glucose levels were significantly decreased at 12 months, but not at 3 or 6 months. The area under the 2-h glucose curve rose slightly at 3 months and decreased slightly at 6 and 12 months, but none of the values were significant.

Konje et al. published three papers using OGTT with an oral glucose load of 75 g to evaluate carbohydrate metabolism in Nigerian Norplant users [29–31]. Two of these publications report on the same study population with follow-up for 12 months [31] and then through 30 months [30]. Twenty women were recruited and evaluated over an 18 month period. Thirteen of these women continued in the study for 30 months. The mean areas under the 3-h glucose and insulin curves were significantly increased at all time points (up to 42% for glucose and 40% for insulin). Despite these fairly substantial increases, all the changes were within normal limits for healthy women in this population.

In a second study, Konje et al. evaluated 24 women who had used Norplant for 18 to 30 months immediately prior to and 4 weeks after removal, and compared the glucose and insulin areas under the curve (AUCs) with pre-insertion values [29]. The mean AUC for glucose 4 weeks following removal was not significantly different than baseline. The mean AUC for insulin after removal remained significantly greater than the pre-insertion value, indicating that changes in insulin sensitivity that may be induced by Norplant were slower to return to pre-insertion values. Differences in the glucose results reported in the two studies of Nigerian women may relate to differences in methodology [28,31]. One group used more restrictive inclusion/exclusion criteria and more clearly defined their methodology for conducting the OGTT [31].

Biswas et al. evaluated 40 Norplant users at a single center in Singapore at 6, 12, and 24 months after insertion using an OGTT with an oral glucose load of 75 g [32]. Consistent with the reports of Konje et al. [30,31], Biswas et al. reported no significant change in fasting glucose values, but reported a significant increase in the mean AUC for both glucose and insulin at all time points. At 24 months, the increases were 70% and 90% for glucose and insulin, respectively.

Singh et al. conducted OGTTs in 100 Norplant users in Singapore over a 5-year period of use. They reported a significant increase in one-hour glucose levels following administration of 50 g oral glucose during the first 2 years of use, but no change in baseline fasting or 2-h glucose levels. Results at 3, 4, and 5 years were not different than baseline [8,9]. Insulin levels were not reported by Singh et al. The reported changes in 1-h glucose test are consistent with those of Konje et la., although less pronounced [29–31]. Again, methodology may explain these differences in that Konje et al. used a 75-gm glucose load whereas Singh et al. used a 50-gm glucose load for the OGTT.

Koopersmith and Lobo evaluated the impact of Norplant on ITTs [33]. The ITT is one of several tests thought to be a more precise measure of insulin action than the OGTT. Ten women from the US were evaluated at baseline and 12 weeks after Norplant insertion. Neither the rate constant for plasma glucose disappearance nor the fractional disappear-

ance rate for plasma insulin differed significantly from baseline values 12 weeks after Norplant insertion.

Shamma et al. [34] conducted hyperglycemic hyperinsulinemic clamp studies in seven US women during the midfollicular phase of a baseline cycle and 8 weeks after Norplant insertion. In this study, fasting glucose levels were acutely raised to 125 mg/dL by infusion of 20% dextrose over a 15-min period. This level was then held constant through measurement and was adjusted every 5 min over the 2-h study period. All women had normal tolerance as assessed by a 75-g OGTT. Fasting glucose and insulin levels were not significantly changed in Norplant users; however, Norplant insertion was associated with a significant increase in first phase insulin response (37%), second phase insulin response (48%), total (2 h) insulin secretion (44%), and total body glucose uptake during the final hour of the clamp (18%). The mean glucose uptake per unit of insulin decreased 17%, with decreases noted in six of the seven women studied, suggesting an impairment in insulin sensitivity. These data are consistent with those of Konje et al. [29–31] and Biswas et al. [32] showing AUCs for glucose and insulin were increased following Norplant insertion.

The inconsistency regarding the impact of Norplant on carbohydrate metabolism may be due to the different methodologies, different follow-up times, as well as differences in the diets and populations studied. As discussed by Shamma et al. [34], the OGTT is poorly reproducible and is a relatively imprecise measure of insulin action because it allows only inferences to be made regarding degrees of insulin resistance. Overall, under certain evaluation conditions and in certain populations, Norplant appears to induce a decrease in insulin sensitivity. Although the reported changes would appear to be clinically insignificant in normal women, no published data address the potential impact of Norplant on insulin sensitivity in diabetic women or in women who may be predisposed to diabetes. If such data could be gathered, they would be valuable in providing evidence to guide clinical practice.

3.3. Hemostasis

Three groups have published seven papers evaluating the effects of Norplant on the coagulation and fibrinolytic systems [35–41]. Like many of the lipid changes, the reported effects of Norplant on hemostatic factors are inconsistent. On balance, however, the limited data are consistent with data on other progestin-only contraceptives that demonstrate minor effects, if any, on hemostasis [1].

Egberg et al. randomized 86 women from Sweden and Finland to either Norplant or Implanon (43 in each group) and followed them for 6 months [35]. Twenty-one tests of possible effects on the hemostatic system were evaluated. Follow-up measurements were compared against the mean of two baseline samples, and changes over time were determined by using the AUC standardized by the length of the study. Ten significant changes in the laboratory tests for hemostasis occurred among Norplant users. The largest percent changes from median baseline levels were a decrease for plasminogen activator inhibitor (PAI-1; 17%) and a decrease for D-dimer (11%, although not significant). Other significant changes in median values, which if considered alone would be in the direction of a potentially greater risk of bleeding, included slight decreases in prothrombin percent activity, Factor VII activity, and α_2-antiplasmin activity and slight increases in median antithrombin III (AT III), protein S free antigen, and plasminogen. Only three significant changes in median values, which if considered alone would be in the direction of a potentially greater risk of clotting, were a slight increase in median fibrinogen and decreases in median activated partial thromboplastin time (APTT) and protein C activity.

In this study, most absolute changes from baseline were very small. Furthermore, the authors stated that the changes noted during follow-up "generally" were not greater than the difference between the two baseline values when examined for each individual patient. This is a key point reflecting the inherent intra-individual variability in these assays and highlighting the strength of their particular study design. Moreover, because a dynamic balance exists between the clotting and fibrinolytic systems, it is impossible to interpret any reported changes in median values of various tests in terms of a potential change in risk to an individual.

Shaaban et al. evaluated hemostatic tests in 47 Norplant users at 1, 3, and 6 months after insertion and compared them with 55 users of oral contraceptive pills [37]. Of the 20 different tests reported, only two were significant when compared with baseline (Factor VII and antithrombin III), but only at the 6-month time point. Factor VII was decreased at 1 month, increased slightly at 3 months, and then increased significantly (12%) at 6 months. AT III was decreased slightly at 1 month, increased slightly at 3 months, and decreased significantly (about 15%) at 6 months. The changes at 6 months for both Factor VII and ATIII were opposite to those reported in Norplant users by Egberg et al. [35]. Furthermore, given the variability over time, it is likely that the significant changes were a chance finding. In contrast, the majority of measurements in the oral contraceptive users at both 3 and 6 months were significantly altered; the changes were greater than any observations in the Norplant group, and except for one factor, the direction of the changes were consistent for both time points.

In a third study, Singh et al. evaluated 23 tests of the hemostatic system in a group of Singaporean women at six time points over 5 years of Norplant use and 6 months after removal [38–41]. Unlike the two studies above, this study did not include a comparison group. Hemoglobin increased significantly at all times relative to baseline. Mean APTT was slightly, but significantly, decreased through 3 years of follow-up. Mean prothrombin time (PT) was slightly, but significantly, decreased at all follow-up times and remained so 6-months after removal. Of the coagulation factors, only

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Factors II and VII showed consistent and significant decreases at all time points; however, neither factor returned toward baseline after Norplant removal. Factor X increased significantly through the 3-year determination. Values in years 4 and 5 were not different than baseline. Other coagulation factors fluctuated around baseline with occasional values being significant. There were no significant changes in fibrinolytic activity and protein (plasminogen activator, fibrinogen degradation products, and plasminogen antigen). AT III antigen and α_2-macroglobulin were increased significantly through 4 years of use, but not in year 5. AT III (functional) was not changed, nor were other coagulation inhibitors (α_2-antiplasmin, α1-antitrypsin, and Protein C). Platelet count, platelet aggregation (+ATP), and platelet aggregation (+collagen) were increased significantly at all follow-up times, and they remained elevated following removal. This group of investigators reported similar effects of Norplant-2 on platelet count [42], but Viegas et al. at the same hospital in Singapore reported no changes in platelets in a study that compared the original Norplant-2 and the reformulated system (Jadelle) several years later [43]. Neither Egberg et al. nor Shaaban et al. reported a change in platelet count during Norplant use [35,37]. Finally, a large, multicenter contraceptive effectiveness study from the People's Republic of China that compared Norplant with Chinese Implant No. I and Chinese Implant No. 2 reported small, statistically, but not clinically, significant increases in platelets for all three groups with no difference across groups [44].

The difference in the findings of Singh et al. compared with those of either Egberg et al. or Shaaban et al. may be due to methodologies (both laboratory tests and study design), the population of women being evaluated, or to chance given the large number of tests and comparisons made. Furthermore, interpretation of the 5-year longitudinal data are difficult given the absence of a comparison group. In this series of articles, presentation of 5-year follow-up and post-removal data for the group of women who actually contributed to all time points would have been useful. Many of the tests reported by Singh et al. were not significantly different 6 months following removal when compared to either the last sample with Norplant in place or to baseline, strongly suggesting no causal relationship between Norplant and the changes reported. In addition, the median values for some tests and the trends in values of others appeared aberrant at certain follow-up times, which is suggestive of a change in laboratory test method or reagents. No comment on potential issues of assay methodology was made in these articles.

In each of these studies, only mean or median values for the various tests were provided. None reported on the number of women who had either increases or decreases in each test over time, particularly during the earlier time points when the release of levonorgestrel is highest. Ranges of individual changes were not presented, nor was information consistently presented on whether any individual participant's test results moved into a range that could potentially impart greater risk for clotting or bleeding. Such information should be provided in future publications.

Overall, it is unlikely that any of the small changes reported in the coagulation and fibrinolytic systems are clinically meaningful. In support of this conclusion, data from the Norplant long-term surveillance study showed no significant excess of myocardial infarction, venous thromboembolism, or stroke in Norplant users compared to women using nonhormonal methods or when compared with the expected number of events based on population-based incidence rates [45,46].

3.4. Liver function

Ten publications that include data from sites in six countries were found specifically reporting on liver function during and following use of Norplant implants [6–10,15, 17,20,35,47]. Five of these publications included sequential data on the same population of users followed over 6 months to 5 years [6–10].

Singh et al. enrolled 100 women, with scheduled follow-up visits at 6, 12, 24, 36, 48, and 60 months and then 6 months after removal [10]. Bilirubin increased significantly by 50% to 60% at all follow-up times and remained elevated by 50% 6 months after removal. A causal association with Norplant is difficult to explain given this latter finding. Total protein and globulin decreased slightly but significantly at 12, 24, and 36 months and were significantly elevated compared to baseline following removal. Despite the significant changes in liver function, no individual value fell outside the normal range for the population. In contrast, Roy et al. reported no changes in liver function tests through 24 months of Norplant use [20]. Mainwaring et al. reported no change in bilirubin in 11 women after 1 year of Norplant use [17]. Shaaban et al. followed 44 women for 6 months and found no clinically important changes in liver enzymes [47]. Bilirubin and bile acids were significantly increased at 1 month, but not at 3 or 6 months. Albumin was elevated at 1 and 3 months, but not at 6 months. Ceruloplasmin was significantly decreased at 6 months, but not at 1 or 3 months. In a cross-sectional study, Croxatto et al. reported no change in total protein, albumin, aspartate aminotransferase (AST), lactate dehydrogenase, alkaline phosphatase, or total bilirubin after about 3 years of Norplant use when compared with IUD users [15].

Egberg et al. evaluated liver function in Norplant versus Implanon users [35]. The exact timing of follow-up evaluations was not stated, however; the implication was that all values were assessed within 6 months of insertion. Increases in total bilirubin and γ-glutamyl transferase and a decrease in AST were observed in both Norplant and Implanon users. The effect of Norplant on bilirubin was significantly greater than that of Implanon. The other changes were not significantly different between the two groups. Only one woman on Norplant had an elevated bilirubin of clinical note (ap-

parently outside the laboratory normal range, although this was not stated). There was no information reported on bilirubin levels following removal of Norplant.

In summary, no clinically important changes in liver function tests occurred in Norplant users. Despite changes in some tests of liver function, values remained within the normal ranges for the populations studied. These data are consistent with studies of the impact of progestin-only pills, in particular those with norgestrel, on liver function [1]. The increase in bilirubin reported in some populations during Norplant use, although not outside the normal ranges for those populations, could become relevant for some individuals. Women admitted to clinical trials are carefully screened to eliminate those at potentially higher risk of disease. Therefore, whether some women in the general population who use Norplant may develop bilirubin changes well above normal is unclear. The recently reported Norplant surveillance study found the rate ratio for gallbladder disease for initiators of Norplant versus initiators of the IUD or sterilization was significantly elevated, although that for current users was not [45,46].

3.5. Blood pressure

No clinically significant changes in blood pressure were reported in prospective clinical trials of Norplant [1,14,20, 21,44,48–51]. In the recently published series of clinical trials comparing Norplant with Implanon, less than 1% of Norplant users had clinically elevated systolic or diastolic blood pressures. The results for Norplant were not different than those reported for Implanon [52]. Shen et al. prospectively followed 267 women using Norplant, 259 women using IUDs, and 238 women starting combined oral contraceptives and found no significant difference between Norplant and IUD users at 1 year [51]. A second study from People's Republic of China comparing Norplant with Chinese Implant No. I reported no clinically significant changes in blood pressure for either group and no difference between the two methods [44]. In contrast to the clinical trial data, the recently published Norplant surveillance study reported an increase in the rate ratio for hypertension and for hypertension combined with borderline hypertension among current users of Norplant compared with controls [46]. The authors state that the higher frequency of hypertension among Norplant users could, in part, reflect reporting bias because blood pressure measurements were more frequent among Norplant participants.

3.6. Other

No clinically important changes in serum chemistry or electrolytes (sodium, potassium, urea nitrogen, calcium, inorganic phosphorus, uric acid) have been reported in studies of Norplant users [2,15,20].

No clinically important changes in thyroid function have been reported in studies of Norplant users. Diaz et al. reported no significant differences in thyrotropin, T3, and T4 levels in Norplant users compared with IUD controls over 36 months [53]. In a comparative study of Norplant and Implanon, Biswas et al. reported no significant changes in mean T3 over a 24-month follow-up period. Mean T4 levels were decreased at 6, 12, and 24 months; however, the baseline values for T4 appeared relatively high and were significantly different than the Implanon group. Thyroid binding globulin (TBG) levels were slightly decreased at 6 and 12 months, but not 24 months. Olsson et al. reported a significant decrease in T4 levels and increase in T3 uptake in Norplant users at 6 months [54]. In a cross-sectional study, Croxatto et al. reported a significant reduction in T3, but no change in T4 levels, after about 3 years of use when compared with IUD users [15]. None of the values were outside the normal range for the general population.

3.7. Summary of metabolic findings related to Norplant

The impact of Norplant on metabolism is small, particularly when compared with changes induced by combined oral contraceptives. The clinical significance, if any, of the reported changes in lipids, hemostatic factors, liver function, or carbohydrate metabolism during Norplant use is unknown. Of great interest to clinicians and users is the question of whether any of the observed changes might predispose a user to increased cardiovascular risk. Data on long-term surveillance of users of Norplant compared with users of IUDs or sterilization are newly available and reassuring [45,46]. This surveillance study included almost 8000 Norplant users who were scheduled to be followed every 6 months for up to 5 years. No significant excess of cardiovascular events such as stroke, myocardial infarction, or venous thromboembolism was observed in Norplant users compared to women using nonhormonal methods or when compared with the expected number of events based on population-based incidence rates. Data from other studies sponsored by the Population Council that include over 9000 women-years of observation document a very low mortality rate in Norplant users, approximately one-sixth the mortality rate expected in the general population of similar age [55]. Similarly, in a 5-year evaluation of Norplant in the People's Republic of China with nearly 45000 women-years of accumulated data, mortality rate was very low, and there were no cardiovascular or cerebrovascular deaths [56].

4. Jadelle

Jadelle, formally called Norplant 2-rod system, consists of two Silastic rods, each with a diameter of 2.4 mm and a length of 44 mm, containing 70 mg of levonorgestrel for a total of 140 mg levonorgestrel. The initial release rate is approximately 80 μg/day, reaching a rate of approximately 30 μg/day after 18 months. The system is labeled to provide

contraceptive protection for 3 years; however, recent data suggest that the system should last 5 years or longer.

The Chinese No. 2 implant system or Sino-implant (Dahua Pharmaceutical Plant, Shanghai, People's Republic of China) is a Silastic two-rod system that contains a total of 150 mg levonorgestrel. It was designed to be nearly identical to the Jadelle system. Data on the metabolic effects of Sino-implant are included in this section.

4.1. Lipid effects

Five groups in four countries have published data evaluating the effects of Jadelle on lipids [20,57–64]. Five of these publications included sequential data on the same population of users followed from 6 months to 5 years [60–64]. There is one small study regarding the effect of Sino-implant on lipids [65].

Total cholesterol levels tended to decrease during Jadelle use [20,58,59,61,63,64]. In the longitudinal study with 5-year follow-up, total cholesterol levels were decreased to a greater extent during the earlier follow-up periods and were not significantly different from baseline in years 4 and 5 [61]. Only one study reported no significant change in total cholesterol [57]. Finally, in the one study that reported lipid levels following removal, total cholesterol returned to baseline levels 6 months post-removal and was comparable to the levels reported at 4 and 5 years [62]. Based on the overall results reported, Jadelle appears to cause a slight decrease in total cholesterol. In contrast, the one study of Sino-implant reported no significant change in total cholesterol at four times over 1 year [65].

Triglycerides decreased significantly during the first 2 years of follow-up in most studies [58–64]. Roy et al. reported a significant decrease only at 6 months with nonsignificant decreases at 12 and 24 months [20]. Bala et al. reported no change in triglycerides at any time point [57]. In the 5-year follow-up study by Singh et al., significant decreases in triglycerides were reported at all but the 4-year point. The levels returned to baseline 6 months after removal [62]. Based on the overall results reported, Jadelle appears to cause a slight decrease in triglycerides that returns to baseline following removal. The one study of Sino-implant also reported decreases in triglycerides during the first year of use [65].

Reports of changes in LDL during Jadelle use are slightly more variable than those for either total cholesterol or triglycerides. Two groups reported significant decreases in LDL during the first year of use [58,64]. In the long-term, follow-up study of Singh et al., the levels remained significantly decreased for 3 years and then returned to baseline levels in years 4 and 5 [61]. Two groups of investigators reported no change in LDL levels [20,59], whereas one group reported a slight, but significant, increase at 12 weeks, although not at 18 to 24 months [57]. Overall, it would appear that LDL cholesterol levels do not change or slightly decrease in Jadelle users. Similarly, LDL levels did not change significantly over 1 year in the single small study of Sino-implant [65].

Data on HDL during Jadelle use were variable. In the long-term, follow-up of Singh et al., no changes in HDL were seen at 6 and 12 months; however, significant decreases were seen at 2, 3, and 4 years [61]. This is in contrast to what would be expected with levonorgestrel release rates from Jadelle. Levels were not significantly different than baseline at 5 years or following removal [62]. Others reported decreases in HDL during the first 2 years following insertion of Jadelle, although these were not always significantly different than baseline [20,58,59]. The one study that included a nonhormonal control group, although small, reported decreased HDL at all times between 3 and 24 months [58]. One group reported no change in HDL [57]. Overall, Jadelle appears to produce a slight decrease in HDL levels. In contrast, the one study of Sino-implant did not report changes in HDL, although HDL2 levels decreased, reaching significance at 3 and 12 months [65].

With regard to HDL to cholesterol ratio during Jadelle use, 2 groups reported no change [57,58], whereas Singh et al. reported significant changes that were in different directions over time [62]. The one study of Sino-implant reported no change in HDL to cholesterol ratio at three of four follow-up times [65]. Given these limited results, firm conclusions about HDL to cholesterol ratio changes with Jadelle or Sino-implant are not possible; however, it is likely that any changes are small.

Three groups evaluated very low density lipoproteins during Jadelle use. One reported no change [57], and two reported significant decreases at some follow-up times [58, 59]. Only one group evaluated apolipoproteins [59]. They reported significant declines in apolipoprotein AI at 6, 12, 18, and 24 months and significant decreases in apolipoprotein B at 12 and 18 months. This study was small and did not include a nonhormonal comparison group. The one study of Sino-implant reported significant decreases in Apo AI at 1, 3, 6, and 12 months with no changes in Apo AII or Apo B [65].

In summary, the decreases in total cholesterol and triglycerides reported in Jadelle users are consistent with those seen in Norplant users. The tendencies toward a decrease in HDL cholesterol is also similar to what was seen for Norplant. As discussed above for Norplant, although decreased HDL may raise the theoretical concern about potential for increased cardiovascular risk, the observations that the HDL to cholesterol ratio changes little, if any, and that triglycerides decrease substantially are reassuring. Although the data are limited for Sino-implant, they are not out of line with the findings on Jadelle or Norplant as might be expected given the similarity with these other methods.

4.2. Carbohydrate metabolism

Five papers from two studies reported information on OGTTs conducted at baseline and up to 5 years following the insertion of Jadelle. Slight and significant increases in

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1-hour glucose levels were consistently reported up to 3 years post-insertion [60,63,64]. These slight increases were not of progressive magnitude over time and returned to normal in the fourth and fifth years post-insertion [61]. No significant differences were reported in 2-h glucose levels in either study [57,61]. The authors concluded that the observed changes were minimal and not likely to be clinically meaningful. The OGTT data reported were all from normal, healthy women. In contrast to Norplant, no data have been published using alternative tests such as the ITT or hyperglycemic clamp to evaluate carbohydrate metabolism or insulin sensitivity among Jadelle users. Given that the two systems are similar in terms of levonorgestrel release rates, one would expect comparable results to those with Norplant. No data have been published evaluating carbohydrate metabolism in women who are diabetic or might be at risk of diabetes using Jadelle.

4.3. Hemostasis

The data on changes in hemostasis and coagulation factors with Jadelle use come from one Chinese study [66] and two studies in Singapore that were published in six papers [42,43,67–70]. The results were not consistent between the two Singapore studies.

One Chinese study randomized 200 women to either the original Norplant-2 or to the levonorgestrel-releasing IUD [66]. No significant changes in AT III content or activity, plasminogen, or α_1-antitrypsin were seen in Norplant-2 users at 6 or 12 months when compared with baseline.

In a study that was similar to their research with Norplant, Singh et al. evaluated 23 measures of the hemostatic system in a group of Singaporean women at six time points over 5 years of Norplant-2 (the original system) use and 6 months after removal [42]. Sixty-two women of the original 100 enrolled completed 5 years of follow-up. Mean PT and APTT were slightly, but significantly, decreased through 5 and 4 years of follow-up, respectively. Both tests remained significantly decreased 6-months after removal, strongly suggesting there is not a causal relationship between the implants and these changes. Of the coagulation factors, Factors II and VII showed consistent and significant decreases at all time points; however, neither of these factors changed significantly after Norplant-2 removal (i.e., were not different than the 5-year measurement). Indeed, Factor VII decreased progressively over time, and mean values were only 60% of baseline at both 5 years and 6 months after removal. These changes mirrored those reported for Norplant over the same time frame [41] and raise a question of whether the assay was stable over time. Factor V increased during the first year, and then was decreased significantly at years 2 through 5 and following removal. Factor VIII antigen was increased significantly at all time points and 6 months following removal. Plasminogen antigen increased significantly in year 1 and decreased significantly during subsequent years. Antithrombin III antigen and antithrombin III activity were not changed, nor were other coagulation inhibitors (α_2-macroglobulin, α_2-antiplasmin, α1-antitrypsin, and Protein C). Platelet count, platelet aggregation (+ATP), and platelet aggregation (÷collagen) were increased significantly at all but one follow-up time, and they remained elevated following removal. Singh et al. reported similar effects of Norplant on platelet count [41], but, as reviewed below, Viegas et al. at the same hospital in Singapore reported no changes in platelets during a later study that evaluated both the original Norplant-2 and the reformulated system (Jadelle) [43].

The second study from Singapore presented data over 36 months on 33 women (17 randomized to the original formulation of Norplant-2 and 16 randomized to the reformulated system, Jadelle) [43]. The two systems provide similar levonorgestrel release rates. No significant changes occurred in platelets or β-TG, an indicator of platelet activation. Fibrinogen increased at all time points, but this increase was significant at five of the eight times for the original formulation and only two of the eight times for the reformulated system. Factor VII decreased for both systems through 12 months, and then increased compared with baseline from month 18 through 36. The observed change between 12 and 18 months is suggestive of some change in the assay rather than a true physiologic effect. There were no changes in tissue plasminogen activator activity or antigen in either group; however, urokinase-like plasminogen activator and antigen decreased from 3 to 36 months. Mean levels of D-dimer were decreased during the first 18 months in both groups, but not in months 24 to 36. PAI-1 activity was not changed, although mean PAI-1 antigen levels were decreased significantly at several time points.

Jadelle studies from Singapore were difficult to evaluate as reported, and the clinical significance of any of the findings are, therefore, questionable. First, information was lacking about the normal ranges of laboratory tests in this population. As with the Norplant studies discussed above, no information was provided on the number of women and time points where values were above or below laboratory normal ranges (information that might suggest clinically important changes in some women). Second, although mean values were presented, information was not presented for any parameter on the number of women who either consistently increased or decreased over time, information that might indicate a tendency for particular women toward clotting or bleeding. Finally, given that withdrawal of Jadelle followed by reevaluation at a distant point when the drug is absent (6 months) did not lead to the return of many abnormal values to baseline indicates the changes were almost certainly not associated with the use of Jadelle.

The only data on the hemostatic system reported for Sino-implant came from a contraceptive trial that compared 1000 Sino-implant users with similar numbers of users of Norplant and Chinese Implant No. 1 [44]. Only platelet levels were evaluated. Small, statistically significant, but

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not clinically significant, increases in platelet counts were reported for the three groups after 24 months of follow-up.

4.4 Liver function

Jadelle appears to have minimal effect on liver function. Roy et al. reported no change in liver function over a 24-month follow-up [20]. Bala et al. reported no significant changes in AST or alanine aminotransferase (ALT) over 24 months [57]. Singh et al. reported some changes in liver function tests that varied with time [62]. Bilirubin was increased at all time points, although the increases were greatest during the first 3 years of use [61]. Following removal, the levels returned to baseline [62]. This result is similar to that reported for Norplant in the same population; however, in the Norplant group bilirubin levels remained significantly elevated 6 months following removal [10]. In this study, total protein and globulins decreased during the first 3 years of use, and albumin increased during the first 2 years of use but returned to baseline after removal of Jadelle. The individual values for even the significant changes were all within the normal range for this population.

4.5. Blood pressure

There were no clinically significant changes reported in any of the published literature on Jadelle. One study of Sino-implant reported no clinically significant effect on blood pressure and no difference when compared with an IUD control group [71]. A second study from the People's Republic of China comparing Sino-implant with Norplant and Chinese Implant No. 1 reported no clinically significant changes in blood pressure in any group and no difference across the groups [44].

4.6. Summary of metabolic findings related to Jadelle and Sino-implant

Although significant changes in some measurements were reported, Jadelle does not appear to cause any clinically meaningful effects on lipid metabolism, hemostatic factors, liver function, carbohydrate metabolism, or blood pressure. The reported results are similar to those seen with Norplant, as one would expect given the similar release rates of levonorgestrel in these two systems. Available data on Sino-implant are more limited, but where available appear generally consistent with Jadelle. Long-term surveillance data comparable to that now available for Norplant are not yet available for Jadelle or Sino-implant.

5. Implanon

Implanon is a single rod, 4 cm in length and 2 mm in diameter, containing approximately 68 mg of etonogestrel (3-keto-desogestrel) in a polyethylene vinyl acetate copolymer membrane. The duration of action is 3 years. The initial release rate of etonogestrel from Implanon is 60–70 μg/day, and declines to about 40 μg/day at 12 months, to 34 μg/day by 24 months, and to 25–20 μg/day by 36 months [72]. The implant is designed to inhibit ovulation over a 3-year period. Etonogestrel is the biologically active metabolite of desogestrel, a progestin contained in many combined oral contraceptive formulations.

Published studies on the metabolic effects of Implanon are limited (n = 6) [13,18,32,35,52,73]. One of these articles [52] is a meta-analysis of various data from individual studies supported by NV Organon. Four of the 13 studies included in this meta-analysis were designed to evaluate metabolic parameters; however, Edwards and Moore did not report on metabolic effects other than blood pressure. Of the four other studies with data on metabolic parameters, the numbers of participants listed in the Edwards and Moore summary table matched those published in only three of the four cases.

5.1. Lipid effects

Two publications provide data on the effects of Implanon on lipid metabolism [13,18]. Suherman et al. prospectively evaluated 90 Indonesian women randomized to either Implanon (n = 45) or Norplant (n = 45) and compared them to a nonrandomized control group of copper IUD users (n = 45). No significant changes in total cholesterol; triglycerides; HDL cholesterol; LDL cholesterol; HDL to cholesterol ratio; HDL/LDL ratio; or apolipoproteins AI, AII, and B were noted over a 36-month period in the Implanon group. There were only occasional significant differences between the two implant groups, which showed no apparent pattern. Mascarenhas et al. followed 30 Implanon users and 30 Norplant users for 2 years, in a randomized, prospective study, and measured fasting serum apolipoproteins AI, AII, and B every 3 months [18]. Slight decreases in apolipoprotein levels were reported, with the corresponding apolipoprotein AI/B ratio decreasing slightly compared with baseline during the first 12 months; however, statistical testing compared with baseline was not reported. All changes, whether increases or decreases, were less than one standard deviation of the mean baseline concentrations and were within the normal range for the reference laboratory. Based on these two small reports, Implanon does not appear to have any clinically meaningful effect on lipid metabolism.

5.2. Carbohydrate metabolism

In a comparative study of Implanon and Norplant, Biswas et al. evaluated 40 Implanon users at a single center in Singapore at baseline and 6, 12, and 24 months after insertion. They used an OGTT with an oral glucose load of 75 g [32]. No significant change in fasting glucose values were observed; however, significant increases in the mean AUC for both glucose and insulin were seen at all follow-up

times. There was no significant difference between the Implanon and Norplant users. Despite the overall changes, individual values for all measurements only occasionally fell outside the normal laboratory reference range. It would appear that Implanon, like Norplant, may induce mild insulin resistance with no significant change in glucose levels in normal women. There are no published data concerning the potential impact of Implanon on insulin sensitivity in diabetic women or in women who may be predisposed to diabetes. As with Norplant, if such data could be gathered, they would be valuable in providing evidence to guide clinical practice.

5.3. Hemostasis

Implanon appears to have minimal effect on the hemostatic system. Egberg et al. randomized 86 women to either Implanon or Norplant (43 in each group) and followed them for 6 months to evaluate hemostasis and liver function [35]. Twenty-one parameters were evaluated to estimate possible effects on the hemostatic system. Follow-up measurements were compared against the mean of two baseline samples. There were 8 significant changes in the laboratory tests for hemostasis among Implanon users and, as discussed earlier, 10 among Norplant users. Although significant, the absolute changes from baseline were generally very small. Furthermore, the changes noted during follow-up were generally not greater than the difference between the two baseline values when examined on the individual level, suggesting that any effects observed were not causally related to the use of either implant system.

5.4. Liver function

Egberg et al. evaluated liver function over a 6-month period in their study of hemostasis reported above [35]. Increases in total bilirubin and γ-glutamyl transferase and decreases in ALT and AST were observed for both Norplant and Implanon. The effect of Norplant on bilirubin was significantly greater than that of Implanon. The other changes were not significantly different between the two groups. Despite the changes observed, the authors reported that the mean values "in general were well within the laboratory reference range" for all tests, and no individuals using Implanon had clinically noteworthy values. It is unclear whether the increase in bilirubin, although not outside the normal range for this population, could become relevant for some individuals.

5.5. Blood pressure

Edwards and Moore presented a meta-analysis of the impact of Implanon on systolic and diastolic blood pressure across all studies in which blood pressure was reported [52]. In this analysis, clinically elevated systolic blood pressure was defined as an actual value over 140 mmHg and an increase from baseline of >20 mmHg for at least two assessments. A clinically elevated diastolic blood pressure was defined as an actual value over 90 mmHg and an increase from baseline of >10 mmHg for at least two assessments. A clinically elevated systolic blood pressure was seen in 0.7% of women, whereas a clinically elevated diastolic blood pressure was seen in 1% of women. When looking only at comparative studies with Norplant, no difference emerged between the two groups. The reported percentage of women with elevated blood pressure during Implanon use is relatively small. Although no information is available about how these numbers would compare to a nonhormonal control group, Implanon appears to have no clinically important effect on blood pressure.

5.6. Other

Biswas et al. evaluated the effects of Implanon compared with Norplant on selected parameters of thyroid function [73]. No significant changes in T3, T4, and TBG were seen in the Implanon group.

5.7. Summary of metabolic findings related to Implanon

Implanon does not appear to have any clinically meaningful effects on lipid metabolism, hemostatic factors, liver function, thyroid function, or blood pressure. However, the number of studies and overall numbers of women evaluated is limited. Given the expected expansion of Implanon availability worldwide, further studies may be warranted. As suggested for Norplant and Jadelle, information about metabolic changes in women who are considered at slightly elevated risk for cardiovascular disease or diabetes would be valuable.

6. Nestorone implants

Nestorone, formally called ST-1435, is a progestin that has high progestational activity, is devoid of androgenic and estrogenic activities, and is not orally active [74]. Two implant systems containing Nestorone have been evaluated [75]. One system is a single rod implant that is being developed by the Population Council to provide contraceptive protection for up to 2 years. The second system, Elcometrine, is a Silastic capsule that lasts for 6 months. Elcometrine is registered in Brazil for contraception, whereas the Population Council's Nestorone implant system is in Phase II clinical trials. A number of the published studies on metabolic effects of Nestorone implants include data from early versions of these implants. Because the metabolic effects for the two types of systems, as well as the earlier prototypes, were similar, the discussion below combines the results of all.

6.1. Lipid effects

Three published studies provide data on lipid and/or lipoprotein levels during Nestorone implant use [76–78]. No significant effects on cholesterol, lipid subfractions, or lipoproteins were reported in any study.

6.2. Carbohydrate metabolism

One publication provided information on OGTTs in five women during use of a Nestorone implant releasing 120 μg/day [78]. No significant changes in either glucose or insulin responses during the OGTT were reported at 1 and 6 months.

6.3. Clinical chemistry

No significant and persistent alternations in liver function tests or other clinical chemistry were reported across four studies of Nestorone implants [76,77,79,80]. In one study, bilirubin levels were slightly and significantly higher during treatment when compared with baseline or to a control group of IUD users, but no women had values outside the normal laboratory range [76]. In another study, AST was decreased at the 12-month follow-up, but not at any other time point [80]. In a study of 30 women from Finland, transient elevations of δ-glutamyl transferase and ALT were seen in several women, as were transient elevations in potassium, sodium, chloride, phosphate, total protein, urate, bilirubin, and lactic dehydrogenase in a small number of women (1–4 for each item) [77].

6.4. Blood pressure

No significant differences in systolic or diastolic blood pressure were reported during Nestorone implant use [77, 79–83].

6.5. Other

Nestorone does not have any effect on sex-hormone binding globulin (SHBG) or on cortisol binding globulin [79]. No information has yet been published on the effect of Nestorone implants on hematologic parameters.

6.6. Summary of metabolic findings related to Nestorone implants

Based on a fairly limited number of publications and women studied, Nestorone implants do not appear to alter liver function, serum chemistry, lipid or carbohydrate metabolism, or blood pressure. No information is yet published regarding effects on the hematologic system. Overall, the reported impact on metabolic parameters appears to be less than that of Norplant, Jadelle, or Implanon; however, more data are needed before any definitive conclusions can be drawn.

7. Uniplant (Surplant; nomegestrol implant)

Uniplant is a single, 1-year implant that delivers nomegestrol acetate at a rate of approximately 100 μg/day during the first 3 months, declining to about 70 μg/day during months 4 to 12 [84]. A limited number of publications provide information on the metabolic effects of this implant. Indeed, further plans to make this product available have been deferred by the company that holds the patent for nomegestrol acetate [75].

7.1. Lipid effects

Three studies have evaluated lipid effects during use of Uniplant. In a 10-center, nine-country, noncomparative clinical trial of contraceptive effectiveness, total cholesterol and LDL cholesterol decreased significantly, although only slightly (3–4%), at 6 and 12 months [85]. HDL cholesterol increased significantly at 6 months and 12 months. Only a subset of the women in this clinical trial appeared to have participated in the lipid evaluations, but neither this point nor the methodologies for lipid evaluation were described in the paper. In a second small study of 18 Brazilian women, total cholesterol decreased over a 24-month follow-up period, but the decrease was significant only at one time point [86]. No significant changes occurred in LDL, HDL, or triglycerides except at 6 months for HDL (decrease) and at 12 months for triglycerides (increase). These changes were compatible with a chance finding. In a third study of 22 Nigerian women, no significant changes were seen in total cholesterol, HDL cholesterol, or LDL cholesterol. Mean triglycerides decreased significantly in month 1 and increased significantly in month 12 compared with baseline; however, all values were within the normal range for this population [87]. Overall, Uniplant does not appear to have any substantial effect on lipid metabolism, but the extent of evaluation is limited both in numbers of women studied and in diversity of populations included.

7.2. Carbohydrate metabolism

Barbosa et al. reported a slight elevation in fasting glucose between 1 and 24 months that was significant only at months 3 and 6 [86]. All levels, however, were within the normal range. In this same study, no significant changes in fasting levels of insulin or glycosylated hemoglobin were seen. Mean glucose values increased slightly at 6 and 12 months among a subset of participants in the large, multicenter trial; however, no information was provided on methodology and whether the values were fasting levels [85]. These data are too limited to allow any conclusions about

the overall effect of Uniplant on carbohydrate metabolism.

7.3. Liver function

In a small study of 18 women followed at six times over 24 months, no clinically significant changes in ALT, AST, gamma glutamyl-transferase, or bilirubin were noted; however, AST was significantly decreased at three time points and ALT at one time point. Bilirubin was increased at one time point. No levels were outside the normal laboratory range [86]. In the multicenter contraceptive effectiveness trial, both ALT and AST were significantly increased at 6 and 12 months among a subset of participants. Alkaline phosphatase was significantly decreased at 6 and 12 months. In all cases, however, the values remained within the normal range for this population [85]. Overall, these evaluations do not indicate that Uniplant has any major effect on liver function, but the data are limited.

7.4. Blood pressure

Both systolic and diastolic blood pressure were significantly decreased in a large, multicenter trial; however, the decreases were less than 1 mmHg and not of clinical significance [85]. In a single center study in Brazil, a significant decrease in systolic blood pressure, but not diastolic blood pressure, was reported [84]. In a third study, both systolic and diastolic blood pressure were increased slightly at 12 months, but not at 24 months [86]. All values were within a low-normal range for blood pressure. Overall, Uniplant does not appear to have any clinically meaningful effect on blood pressure.

7.5. Other

In the one multicenter clinical trial, urea nitrogen was slightly increased and creatinine slightly decreased at 6 and 12 months; however, none of the changes were outside the normal range for this population [85]. In a small study of 18 women followed up to 2 years, Barbosa et al. reported no effect on thyroid function in Uniplant users [88]. Barbosa et al. also reported no effect on plasma SHBG or free testosterone during Uniplant use, although total testosterone and androstenedione were significantly decreased [89,90]. No information has been reported on the hemostatic system.

7.6. Summary of metabolic findings related to Uniplant

Although the data are fairly limited, Uniplant appears to have minimal effect on the metabolic parameters evaluated to date. Additional studies are needed if this product is to become more widely available.

8. Overall Conclusions

In this review, the metabolic effects of implant systems that deliver five different progestins were evaluated. The metabolic effects of Norplant, Jadelle, and their Chinese equivalents appear to be similar, which is reassuring given their similar levonorgestrel release rates, serum levels of levonorgestrel over time, and clinical performance. The metabolic effects of Norplant were also similar to those of Implanon in all of the studies in which the two products were compared directly. In contrast, the effects of Norplant, Jadelle, and Implanon appear to be slightly greater than those reported for Nestorone implants/Elcometrine and Uniplant. However, the data on these latter systems are much more limited. Furthermore, there were no randomized, controlled trials directly comparing the systems, so this conclusion remains to be validated.

None of the methods appear to have any clinically important effect on blood pressure, an important potential risk factor for cardiovascular disease. This finding is consistent with the lack of effect of other progestin-only preparations on blood pressure, at least in women with normal blood pressures [91]. None of the methods appear to have clinically important effects on liver, kidney, or thyroid function. The only observation of note is the slight elevation of mean bilirubin levels reported in studies of four of the implants (Norplant, Jadelle, Implanon, and Nestorone). The magnitude of the elevation was greatest for the levonorgestrel implants; however, in all cases, values remained within the normal ranges for the populations studied. These data are consistent with studies of the impact of progestin-only pills, in particular those with norgestrel, on bilirubin [1]. Although not outside the normal range, an implant-induced elevation of bilirubin might become relevant for some individuals, e.g., those with a history of pregnancy-induced cholestasis [92] and, therefore, would be of interest to understand better. In the Norplant surveillance study, the rate ratio of gallbladder disease for Norplant initiators was significantly greater than that for IUD or sterilization users, although this was not seen when only current users were assessed [46].

Altered glucose tolerance characterized by decreased insulin sensitivity following glucose administration has been associated with combination oral contraceptives and certain progestin-only contraceptives [1,24]. Under certain evaluation conditions and in certain populations, Norplant, Jadelle, and Implanon led to decreased insulin sensitivity. Insulin resistance has been suggested as one of the mechanisms by which risk of arterial disease is increased [24,91]. Furthermore, a recent report that evaluated insulin resistance as a predictor of age-related diseases found significantly higher disease rates among those with the greatest level of insulin resistance [93]. Data from the Norplant long-term surveillance study are reassuring in this context because no significant excess of cardiovascular events (stroke, myocardial infarction, or venous thromboembolism) were observed in Norplant users compared to women using nonhormonal methods or when compared with the expected number of

events based on population-based incidence rates [45,46]. No long-term surveillance data exist for any of the other methods. No published data concern the potential impact of progestin implants on insulin sensitivity in diabetic women or in women who may be predisposed to diabetes. If such data could be gathered, they would be valuable in providing evidence to guide clinical practice.

Changes in lipids and lipoproteins also appear to be minimal for all methods. In the cases of Norplant and Jadelle in which some changes were consistently reported, one cannot infer that these limited observed changes in mean values for lipids, lipoproteins, and various ratios would translate to any change (increase or decrease) in cardiovascular risk for the population of healthy individuals that was studied. Risk for CHD that is associated with increasing total cholesterol and decreasing HDL is continuous and graded with considerable overlap between the total cholesterol and HDLs distribution of men and women with and without prevalent CHD [27]. Furthermore, other factors, such as triglycerides, modify risk [24,27]. However, as pointed out throughout this article, one should be cautious in generalizing the data from healthy populations to populations with pre-existing cardiovascular disease or even to populations that could be categorized at elevated risk. There are no data in these groups of higher risk women who are often preferentially provided progestin-only methods. If further studies could be conducted ethically, it would be valuable to gather information on the effect of progestin implants on lipid profiles in women thought to be at elevated risk of cardiovascular disease.

None of the implant systems appeared to have a clinically important impact on the clotting or fibrinolytic systems. These data are consistent with data on other progestin-only contraceptives that demonstrate only minor effects on hemostasis. [1].

In conclusion, the growing literature demonstrates minimal metabolic effects of progestin implant systems in healthy populations of users. These changes are unlikely to be clinically important in this group of women. No published data describe metabolic effects of any of the implant systems in women who might be at elevated risk for certain diseases. Given that progestin-only implant systems are recommended over estrogen-containing contraceptives for certain high-risk women who seek a hormonal contraceptives, the field would be well served to have additional empiric data from well-designed, well-implemented, and well-reported trials in women who might be deemed to be at elevated risk for diseases including cardiovascular disease and diabetes.

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