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HUMAN PAPILLOMAVIRUS (HPV) AND CERVICAL CANCER: IMPLICATIONS OF HPV VACCINES

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On June 8, 2006 the FDA announced approval of Gardasil® (gärd' ə sĭl), Quadrivalent Human Papillomavirus (HPV) recombinant vaccine manufactured by Merck. This vaccine, along with Cervarix® (sər vâr' ĭks), which is in Phase III clinical trials by GlaxoSmithKline, has implications for the prevention of cervical cancer, genital warts and precancerous or dysplastic lesions. This article will discuss HPV and its' relation to cervical cancer, as well as the efficacy, duration of protection and place in practice of the HPV vaccine.

Cervical Cancer

According to the American Cancer Society, it is estimated that in 2006 over 9,700 women in the United States will be diagnosed with cervical cancer and 3,700 will die.[11] Worldwide, the numbers of women affected are much greater. Cervical cancer is the 2nd most diagnosed cancer in underdeveloped countries, with approximately 470,000 cases/year, and a 50% mortality rate.[2] After the addition of routine PAP screening, the incidence of cervical cancer has been on a downward trend in the US. Additionally, the economic burden of disease is large: the costs of screening cervical cancer are estimated at $6 million/year and approximately $2 billion/year are spent on treatment.[2]

HPV

HPV is a small, double-stranded, circular DNA virus that infects human basal epithelial cells and is transmitted sexually.[1-3] Approximately 20 million people in the US at any time are infected with HPV.[2,7] Over 100 types of HPV have been identified. Some types, such as type 16 and 18, are higher risk for causing cervical cancer. Low risk types such as HPV 6 and 11 cause 90% of genital warts.[3,6,10] Cervical cancer and HPV infection are highly correlated, with at least 99% of cervical cancers containing HPV of certain high risk types, and approximately 70% containing HPV types 16 or 18.[2,6,9,12] HPV leads to cervical cancer by infecting the cervical epithelium during sexual intercourse. Infection by the virus leads to viral replication and shedding that results in epithelial changes. HPV oncogenes E6 and E7 act to deregulate the cell cycle of normal cells and can lead to cancerous lesions by offering infected cells a growth advantage, introducing defects in differentiation, increasing the probability of mutation and creating genomic instability.[2,5] A vaccine that would protect against high risk types of HPV would be beneficial in reducing the incidence of cervical cancer.

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The vaccines that are on the market or in Phase III clinical trials are classified as prophylactic vaccines. They work by utilizing the major capsid protein of the HPV virus (L1), which self-assembles into virus-like particles (VLP's) that are empty capsids. The VLP's contain no viral DNA and are thus noninfectious. VLP's are so similar to HPV virions that they are effective in stimulating an antibody response. Gardasil® is the first HPV vaccine approved to prevent cervical cancer and genital warts. It is a quadrivalent vaccine that targets HPV types 6, 11, 16 and 18 by containing VLP's of each HPV type. It contains amorphous aluminum hydroxyphosphate sulfate as an adjuvant.[4] Cervarix® is a bivalent vaccine targeting HPV 16 and 18. It contains a new adjuvant, aluminum hydroxide with 3-decylated monophosphoryl lipid A, that may offer an advantage by producing higher antibody titers than the aluminum salt alone, leading to an enhanced immune response.[7] Phase II studies compared the new adjuvant to the aluminum salt formation and found a 1.6 to 3.2 fold increase in antibody response with the new formulation. [17]

Clinical trials

Efficacy trials

Gardasil® was evaluated in 4 placebo-controlled, double-blind, randomized Phase II and III clinical trials. The Phase III trials were termed FUTURE I and FUTURE II (Females United to Unilaterally Reduce Endo/Ectocervical Disease.) FUTURE I administered Gardasil® or placebo to 5,455 women, and FUTURE II evaluated 12,157 women. In both trials, women aged 16-26 received vaccination or placebo on day 1 and at months 2 and 6. Co-primary endpoints were combined incidence of HPV 6,11,16 or 18-related cervical dysplasia, adenocarcinoma in situ (AIS), and combined incidence of HPV 6,11,16 or 18-related condyloma (genital warts), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VAIN), and vulvar or vaginal cancer. Presence was detected by PAP smears taken at day 1, month 7, month 12, and 6 month intervals up to month 48. Genital tract specimens were also obtained at day 1 and months 3 and 7. The per-protocol population included subjects who received all 3 vaccinations within 1 year of enrollment, had no major protocol deviations, and were HPV naïve. FUTURE I and II found 100% efficacy ($p<0.001$) in preventing HPV 16 or 18 related CIN or AIS. FUTURE I found Gardasil® to be 100% effective ($p<0.001$) in preventing HPV 6,11,16 or 18-related CIN, AIS, condyloma, and vaginal/vulvar lesions, and FUTURE II found 90.7% efficacy ($p<0.001$) for this endpoint.[16,4] It is unknown why FUTURE II had lower efficacy than previous phase II and III trials that showed 100% efficacy. In a combined analysis of the placebo groups in phase II and III studies, 83 of 7861 subjects experienced HPV 6,11,16,or 18 related CIN or AIS as opposed to 4 of 7853 subjects in the treatment group. [4]

A double-blind, multi-center, randomized, placebo-controlled trial was performed to assess the efficacy of the bivalent HPV 16 and 18 vaccine Cervarix®. The study administered the vaccine at day 1, month 1 and month 6 and included women aged 15-25. Cervical samples for HPV testing were collected at months 6, 12 and 18, and immunogenicity was assessed at months 0,1,6,7,12 and 18.The primary endpoint was effectiveness at preventing infection with HPV 16 or 18 in patients not infected at baseline. Secondary outcomes were prevention of persistent HPV 16 and 18 infection, squamous epithelial lesions, cancer or adenocarcinoma.[15] Follow-up continued until month 18 and extended follow-up was performed until month 27. In the per-protocol analysis, study results found 100% efficacy ($p<0.0001$) of the vaccine against persistent HPV 16 and 18 infection. The vaccine was also effective at preventing 93.5% of HPV-related cytological abnormalities.[15] An intention-to-treat (ITT) analysis was performed in participants who did not follow study protocol but received at least 1 dose of the vaccine. In the ITT analysis, 84.5% ($p<0.0001$) of patients were protected against HPV 16 and 91.1% ($p=0.003$) effective against HPV 18. Efficacy in preventing cervical HPV 16 or 18 persistent infection was 95.1% ($p<0.0001$) and abnormal cytology was prevented in 92.9% ($p<0.0001$). [15]

Both HPV vaccines are considered prophylactic. In Gardasil® trials, there was no evidence that the HPV vaccine provided any protection against HPV types covered by the vaccine that study subjects had already contracted.[4] However, if a subject was infected with one particular HPV type at baseline, the vaccine offered protection against other types of HPV included in the vaccine.[4] Thus, while individuals not yet exposed to HPV benefit most

Table 1. Summary of clinical trials evaluating HPV vaccines

Study	FUTURE[a] I [16]	FUTURE II [4]	Harper [15]	Harper followup [8]
HPV subtypes in vaccine	6, 11, 16, 18	6, 11, 16, 18	16, 18	16, 18
Design	Randomized, Double-blind, controlled	Randomized, Double-blind, controlled	Randomized, Double-blind, controlled	Randomized, Double-blind, controlled
Age (N)	16-26 (5455)	16-26 (12157)	15-25 (1113)	15-25 (776)
Adjuvant	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxide and 3-decylated monophos-phoryl lipid (ASO4)	Aluminum hydroxide and 3-decylated monophos-phoryl lipid (ASO4)
Schedule	0,2, and 6 months	0,2, and 6 months	0,1 and 6 months	0,1 and 6 months
Median follow-up	29 months	24 months	27 months	42 months
%Efficacy vs. HPV 16/18	100%	100%	100%	100%
%Efficacy vs. preventing cytological abnormalities	100%	90.7%	93%	92.6-100%
% Efficacy preventing genital warts	100%	98.3%	NR	NR
Adverse Events	Nonsignificant	Nonsignificant	Nonsignificant	Nonsignificant

[a] FUTURE= Females United to Unilaterally Reduce Endo/Ectocervical Disease HPV= Human Papillomavirus; NR=Not Reported; N=number of subjects

from receiving the vaccine, there is still an indication for its' use in those who have already been exposed. A summary of the clinical trials is presented in Table 1.

Duration of protection

Trials have assessed the efficacy of the HPV vaccine in the short term, therefore it is possible that individuals will need booster shots over the years to maintain high antibody titers. A follow-up study of the multicenter, double-blind, randomized, placebo-controlled trial evaluating Cervarix® was performed to assess vaccine efficacy over an extended period of time.[8] Women that originally received all three doses of the vaccine were included in the extended follow-up (393 in the vaccine group and 383 in the placebo group.) Cervical samples were collected every 6 months. The primary endpoint was long-term vaccine efficacy in the prevention of HPV 16 and 18 infection. Secondary endpoints assessed were HPV 16 or 18 infections persistent for 6 and 12 months, and squamous intraepithelial lesions, atypical squamous cells, and atypical glandular cells. Analysis of antibody titers showed over 98% of women remained seropositive for HPV 16 and 18 at all time points during the follow-up period of 42 months. The study found that 100% vaccine efficacy remained against all HPV 16 and 18 related histological abnormalities. This follow-up study demonstrates that the vaccine can be effective against incident and persistent infections of HPV 16 and 18 for a period of at least 4.5 years.

Gardasil® trials also assessed antibody titers through 36 months. A study assessing immunologic responses in the first phase II trial was performed. At 36 months post-dose, 94%, 96%, 100%, and 76% of women in the per-protocol population remained seropositive for HPV types 6, 11, 16 and 18, respectively.[14] While the geometric mean titers (GMT) of all subjects decreased for each time point (months 7, 24, and 36), titer levels became more stable between months 24-26 and remained positive through 36 months.[4,14] It was also noted that antibody levels post-vaccination were comparable to those of a natural infection.[14]

While it is possible that the novel adjuvant in Cervarix® may offer a titer advantage over the adjuvants of other vaccines, GMT's were not reported in the Cervarix® trial so a direct comparison is not possible. Also, minimum antibody levels needed for disease protection have not been established because there were few disease cases in those seronegative at baseline. Since women will be receiving the vaccine at a very young age, continued follow-up and more

clinical trials will be needed to confirm duration of protection.

Dosage and Administration

Gardasil® is administered intramuscularly in a series of three 0.5 ml doses. The second and third doses are given 2 and 6 months after the first dose.[4] Cervarix® is administered in 3 doses, with the second and third doses given at 1 and 6 months after the first dose.

Clinical trials studied women aged 15-26, yet the vaccine is indicated for girls ages 9-26. Younger ages were included as a result of a study that compared anti-HPV titers one month after the last Gardasil® dose in 9-15 year old girls and 16-26 year olds.[4] It found that anti-HPV responses in ages 9-15 were non-inferior to responses of 16-26 year olds, so efficacy of Gardasil® in ages 9-15 is inferred. The Advisory Committee on Immunization Practices recently recommended its' addition to the vaccination schedule for all girls ages 11-12.

Toxicity and Safety

Adverse reactions to Gardasil® were mild compared to placebo, with the most common reactions consisting of injection site reactions, pyrexia, nausea, nasopharyngitis and dizziness. Injection-site reactions were judged by 94.3% of patients as mild or moderate intensity. The incidences of overall adverse reactions were low and comparable to placebo. (**Table 2**) Gardasil® is not recommended for use in pregnancy, and is rated pregnancy category B. It is unknown if the vaccine is excreted in breast milk, and thus it is recommended that caution should be used when administering the vaccine to nursing mothers.[4]

Table 2. Most common vaccine-related adverse reactions [4]

Adverse Reactions	Gardasil® (%)	Placebo (%)
Injection Site		
Pain	83.9	75.4
Swelling	25.4	15.8
Erythema	24.6	18.4
Pruritis	3.1	2.8
Fever	10.3	8.6
Nausea	6.7	6.6
Nasopharyngitis	6.4	6.4
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Myalgia	2.0	2.0
Cough	2.0	1.5

Cost

Gardasil® is currently the most expensive vaccine on the market, twice the cost of other 3-dose vaccines.[13] Each dose is $120, for a total of $360 for the series. Cost data is not currently available for Cervarix®. Due to the recent approval and high cost, it is uncertain when insurance companies will begin covering the vaccine. Some major insurance carriers already offer coverage, but most companies have yet to make a decision. It is expected that many will begin offering coverage in the next year.[13] If officially included in the CDC's routine vaccination schedule, Gardasil® will be automatically included in the federal Vaccines for Children Program that provides vaccines free to uninsured children or those on Medicaid. Many private insurers also use the recommended vaccination schedule to make coverage decisions.

Summary

HPV is a highly prevalent sexually transmitted virus with low risk subtypes that result in up to 90% of genital warts, and high risk subtypes that can result in cervical cancer. Cervical cancer is highly correlated with the presence of the HPV virus as indicated by the presence of HPV in approximately 99% of all cervical cancers. Gardasil®, a new preventative HPV vaccine was recently approved by the FDA. Another HPV vaccine, Cervarix®, is currently in Phase III clinical trials. These vaccines show up to 100% efficacy at preventing HPV 16 and 18 related cervical cancer and have a favorable safety profile. With the introduction of these vaccines, there is promise for decreasing HPV infection and cervical cancer death rates.

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IMPLANON®: A REVIEW

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Contraceptive use in the United States is virtually universal among women of reproductive age. Statistics show that 98% of all sexually experienced women had used at least one contraceptive method. The leading method of contraception in the United States in 2002 was the oral contraceptive pill. It was being used by 11.6 million women 15–44 years of age. The second leading method was female sterilization or tubal ligation; used by 10.3 million women.[1,2] Choosing a method of birth control is a highly personal decision, based on individual preferences, medical history, lifestyle, and other factors. Although there are many options for contraception use, implantable devices are one of the least used methods due to lack of knowledge, fear of side effects, or an existing satisfaction with current techniques.

Until now, there was one implantable contraceptive device in the United States. Norplant®, a levonorgestrel implantable device, approved by the FDA in December of 1990, consisted of six, 36mg slow release capsules that provided protection for 5 years. Due to problems with removal of the implants and high numbers of reported ADRs, it was discontinued in 1996.

Etonogestrel implant (Implanon®[ĭm' plə nôn]) is the newest progestin-only implantable contraceptive device that was approved by the FDA on July 17, 2006. Unlike Norplant®, etonogestrel implant (ENG implant) consists of a single rod; each containing 68mg of etonogestrel. ENG implant achieves a contraceptive effect by mechanisms that include suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.[4] It is manufactured by Organon USA Inc. and is expected to be widely available in the U.S. by 2007. This article will review the pharmacology, administration, safety, and efficacy profile of the ENG implant.

Pharmacology/Pharmacokinetics

ENG implant is a single nonbiodegradable rod, about the length of a toothpick (4 cm x 2 mm), consisting of 40% ethylene vinyl acetate (EVA) and 60% ENG, containing a total of 68 mg of ENG. Each rod is surrounded by an EVA copolymer membrane (0.06 mm thick) that controls the rate of release of ENG over a span of 3-years. Throughout the first two years, 100% bioavailability is achieved by a constant release of ENG. The 68 mg of ENG contained in the rod is initially absorbed at a rate of 60 µg per day, slowly declining to 30 µg per day after 2 years. Peak serum concentrations (266 pg/mL) of ENG are achieved within 1 day after insertion, effectively suppressing ovulation (which requires 90 pg/mL ENG or more). The steady release of ENG into the circulation avoids first-pass effects in the liver. The elimination half-life of ENG is 25 hours and is mainly excreted in the urine and to a lesser extent in feces.[4] After removal of the device, serum ENG concentrations become undetectable within 1 week, and ovulation resumes in 94% of women within 3 to 6 weeks.[5] Similar to other contraceptive steroids, cytochrome P450 inducing drugs, such as rifampin, griseofulvin, phenylbutazone, phenytoin, and carbamazepine, may decrease serum levels of ENG, decreasing efficacy.

Administration

Timing

Timing of the ENG implant insertion depends on the patient's recent history of contraceptive use. The most important rule before inserting the implant is to rule out pregnancy. For women who have not been using contraception or who have been using a nonhormonal method, the implant is inserted between days 1 and 5 of menses. For women changing from a combination or progestin-only oral contraceptive, the implant is inserted any time during active treatment. If a woman is changing from an injectable contraception, the implant is inserted on the date of the next scheduled injection. Lastly, for women using an intrauterine device (IUD), insertion can take place at any time.[5]

Insertion and Removal

ENG implants will be available to all patients seeking a more convenient and discreet form of birth control, however; only physicians who undergo specialized training will be able to administer the device. Subdermal placement is imperative for efficacy and easy removal, therefore; the implant comes preloaded with all equipment necessary to reduce the risk of accidental placement in muscle tissue. The insertion process takes on average 1.4 $\pm$ 1.7 minutes.[9] Once inserted, the implant may not be visible but must remain palpable to ensure the 4 cm rod is correctly in place. In addition, it is important to advise all patients to use a second form of birth control, such as a condom or spermicide, for 7 days following insertion to protect against any failure of the implant.[5]

The ENG implant can be removed at any time, but will remain effective for 3 years if left in place. Removal requires a 2-mm incision at the distal tip of the implant and takes about 2.5 to 5.5 minutes.[3] Common reactions that may occur after insertion or removal of the procedure are pain, swelling, redness, and hematoma. Because ovulation resumes rapidly following removal, women still desiring contraception should begin another method immediately or have a new rod inserted through the removal incision.[5]

Clinical Trials

The efficacy of the ENG implant has been studied in various trials. Trials have been performed studying the effects of ENG implant on metabolic processes; including lipid profiles and liver function tests, and against a similar progestin-only implant.

Lipids

The effects of Implanon® and Norplant® implants on serum lipids over 2 years of use was assessed in an open, randomized study. Study subjects (N=80), divided into 2 groups, were sexually active between the ages of 18 and 40 years old. Serum lipids were obtained preinsertion and after 6, 12, and 24 months of use. The lipid parameters evaluated were: TC, HDL, LDL, TGs, apolipoprotein A-1 and B. At the end of 2 years, TC, HDL, and LDL were significantly decreased in the Implanon® group (p-values 0.000, 0.026, 0.027 respectively); whereas TC, LDL, and TGs were significantly reduced in Norplant® users (p-values 0.000, 0.020, 0.000 respectively). TGs were slightly increased by 2.25% in Implanon® users, but was not statistically significant. In both groups, there was a significant increase in apolipoprotein B at the end of the 24 month period. Overall,

the study showed reductions in all lipid parameters for each group; however, there was no significant difference between the implant groups at any time period (**Table 1**).[6] Since the study population included subjects with higher BMIs and preinsertion lipid levels, we can presume these implants have a beneficial effects on lipid parameters in hyperlipidemic patients.

Liver Function Tests

In the same 2-year open, randomized, comparative study (N=80), change in liver function parameters: total bilirubin, unconjugated bilirubin, albumin, AST, ALT, GGT, and lactate dehydrogenase (LDH) were assessed on subjects receiving either implant. Blood samples were taken preinsertion and after 6, 12, and 24 months. In both implant groups, the most significant change was in total bilirubin and unconjugated bilirubin levels. At the end of 2 years, the mean unconjugated bilirubin levels were more than seven fold greater than the mean preinsertion levels for users of both types of implants (Implanon®: 1.17 µmol/L vs. 8.32 µmol/L, $p \leq 0.000$; Norplant®: 1.25 µmol/L vs. 8.25 µmol/L, $p \leq 0.000$). However, the total and unconjugated bilirubin levels did not exceed the normal range at any point during the study. In the Norplant® group, ALT levels were significantly decreased (23.80 U/L vs. 18.93 U/L, $p \leq 0.008$) while AST and LDH levels were significantly increased in the Implanon® subjects during the first year of use, which gradually returned to baseline at the end of 2 years. In both groups, the GGT levels were significantly raised during treatment period (Implanon®: 25.05 U/L vs. 33.10 U/L, $p \leq 0.000$; Norplant®: 18.60 U/L vs. 24.83 U/L, $p \leq 0.000$).[8] There were no significant changes in serum albumin. To a healthy user of either implant, there are no adverse effects related to hepatic dysfunction, however, caution should be used in patients with preexisting liver disease (**Table 2**).

Bleeding Patterns

Irregular bleeding problems tend to be the most common adverse effect among progestin-only methods of contraception. The efficacy and bleeding patterns of Implanon® and Norplant® were studied in an open, comparative, randomized, multicenter trial. Two hundred healthy, sexually active women received either a single-rod Implanon® or six capsule Norplant® for 2 years. The study was extended up to

Table 1. Changes in serum lipids between Implanon® and Norplant® users.[6]

Parameter (mmol/L)	Implanon® (N=40)			Norplant® (N=40)			Group Comparison of mean (p-value)
	Mean (mmol/L)	% change from baseline	p-value	Mean (mmol/L)	% change from baseline	p-value	
Total Chol.							
Baseline	5.36			5.49			0.198
6 months	4.88	-7.16	0.000	4.63	-14.75	0.000	0.206
12 months	4.82	-8.27	0.000	4.69	-14.07	0.000	0.470
24 months	4.72	-8.85	0.000	4.78	-10.65	0.000	0.786
HDL							
Baseline	1.38			1.30			0.278
6 months	1.24	-9.24	0.000	1.14	-9.1	0.000	0.051
12 months	1.23	-9.59	0.001	1.12	-11.94	0.000	0.050
24 months	1.27	-5.78	0.026	1.21	-3.24	0.087	0.246
LDL							
Baseline	3.55			3.75			0.397
6 months	3.38	-2.58	0.049	3.25	-11.73	0.000	0.581
12 months	3.40	-2.48	0.232	3.36	-9.43	0.000	0.811
24 months	3.19	-5.87	0.027	3.35	-6.9	0.020	0.698
Triglycerides							
Baseline	0.88			1.09			0.013
6 months	0.82	-1.55	0.065	0.73	-26.89	0.000	0.444
12 months	0.78	-6.09	0.014	0.73	-30.25	0.000	0.201
24 months	0.86	2.25	0.795	0.80	-22.27	0.000	0.265

4 years after data showed ovulation remained suppressed after 2 years. Overall results showed fewer frequent bleeding patterns in the Implanon® group. The incidence of amenorrhea and infrequent bleeding, defined as < 2 bleeding/spotting episodes per reference period (90 days), was higher in the Implanon® group. In a given reference period, amenorrhea occurred in 2.0%–18.6% of the women in the Implanon® vs. 1.0%–6.2% of women in the Norplant® group. Results of infrequent bleeding in the 2 groups were 8.4%–26.0% (Implanon®) and 5.0%–13.7% (Norplant®). In general, lower incidence of frequent bleeding, > 4 bleeding/spotting episodes, were observed in the Implanon® group. Frequent bleeding ranged between 1.3% - 10.4% in the Implanon® group compared to 2.3% - 13.0% in the Norplant® group. The mean overall incidence of prolonged bleeding, ≥ 1 bleeding/spotting episode lasting ≥ 10 days, fell dramatically during the study, with Implanon® ranging from 66% in the first reference period to 27% in period 16, and with Norplant® from 69% to 22% (**Figure 1**). Efficacy was based on the occurrence of in-treatment pregnancies, which was zero in both treatment groups.[10]

Safety and Efficacy

Safety of the ENG implant has been investigated in several trials. In one study, the most common adverse event reported in patients was infrequent bleeding, defined as less than three bleeding/spotting episodes in a reference period (90 days), excluding amenorrhea. The least common pattern was frequent bleeding, or more than five episodes of bleeding in a reference period. Infrequent, prolonged and frequent bleeding patterns were most common during the first 8 months of the study and declined thereafter. During months 4–24, the incidence of amenorrhea ranged from 14% to 20%. Forty-three subjects (13%) withdrew from the study because of bleeding pattern changes and 76 subjects (23%) discontinued because of other AEs: emotional lability (6.1%), weight increase (3.3%), depression (2.4%) and acne (1.5%).[7] Side effects that have been reported from a combination of clinical trials (942 subjects) include headache (24.9%), vaginitis (14.5%), breast pain (12.8%), and upper respiratory tract infection (12.6%).[4]

Cost

The cost of Implanon® has not yet been determined; however it is assumed that it will be comparable to the monthly cost of other contraceptive methods.

Summary

Overall, the ENG implant is a highly acceptable, excellent contraceptive alternative in patients who are searching for a long term, disguisable birth control method.[11] By maintaining a sustained release of progestin, it is independent of user compliance, which is a factor in the efficacy of most contraceptive methods.[10] In clinical trials, the implants have minimal metabolic effects and decreased bleeding episodes over time.[6,8,10] By providing 3 years of contraception and a rapid return of fertility after removal, the ENG implant is a tolerable and effective contraceptive alternative.[10]

Table 2. Changes in Liver Function Tests between Implanon® and Norplant® users.[8]

Parameter	Sample times	Implanon® (N=40)			Norplant® (N=40)			Group Comparison of mean (p-value)
		Mean	% change from baseline	p-value	Mean	% change from baseline	p-value	
Total bilirubin (µmol/L)	Baseline	3.42			2.25			0.001
	24 mo.	9.32	196.01	0.000	9.26	317.20	0.000	0.975
Unconjugated bilirubin (µmol/L)	Baseline	1.17			1.25			0.794
	24 mo.	8.32	720.09	0.000	8.25	758.33	0.000	0.975
ALT (U/L)	Baseline	23.80			23.80			0.546
	24 mo.	22.89	2.60	0.687	18.93	-15.83	0.008	0.041
AST (U/L)	Baseline	21.30			21.60			0.334
	24 mo.	20.59	5.23	0.402	21.77	4.67	0.749	0.367
GGT (U/L)	Baseline	25.05			18.60			0.039
	24 mo.	33.10	36.06	0.000	24.83	38.28	0.000	0.229
LDH (U/L)	Baseline	449.35			387.97			0.006
	24 mo.	436.05	2.43	0.441	401.90	2.74	0.890	0.010

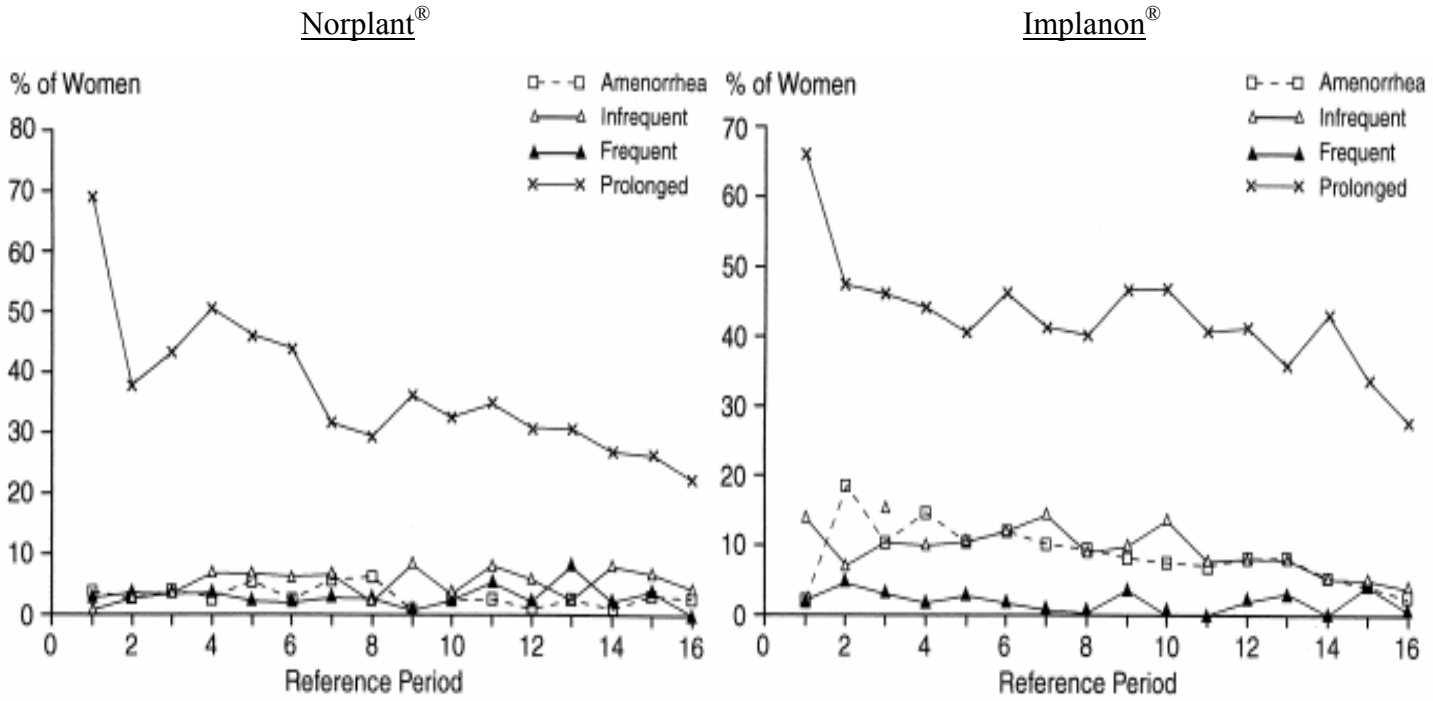

Figure 1. Percentages of women reporting amenorrhea, infrequent, frequent, and prolonged bleeding in the Norplant® and Implanon® groups.[10]

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