

Progestin-Only Injectables (DMPA and NET-EN)

Q.1. When can the first progestin-only injection be given (interval)? How soon does it become effective? Is a back-up method needed?

Recommendations	Rationales
<p>a) Progestin-only injections may be given any time you can be reasonably sure the woman is not pregnant, for example, during the 7 days which begin with the onset of menses (days 1 through 7 of the menstrual cycle).</p>	<p>a) Although ovulation can occur as early as day 10 of the menstrual cycle, this is rare⁴. Fertile ovulation is very uncommon before day 12¹. Intercourse 5 days before ovulation may have as much as a 5% chance of resulting in pregnancy²; however, since experts believe there are few fertile ovulations before day 13, there is only a very small chance that intercourse on day 7 of the cycle could result in pregnancy¹.</p> <p>In general, use of DMPA within the first 7 days after the woman's normal menses would assure that the probability of the woman already being pregnant, or becoming pregnant, is extremely low³.</p> <ol style="list-style-type: none">1) The Technical Guidance Working Group has reached this conclusion after a thorough review of the available literature and consultation with the following experts: William Collins, PhD, DSc, Department of Obstetrics and Gynecology, Kings College, UK Jeffrey Spieler, MSc, Research Division, Office of Population, USAID.2) Dixon GW, Schlesselman JJ, Ory HW, Blye RP. Ethinyl estradiol and conjugated estrogens as postcoital contraceptives. <i>Journal of the American Medical Association</i> 1980;244:1336-1339.3) Gray RH, Pardthaisong T, McDaniel EB, Doyle P. The timing of the first injection of Depo Provera. <i>IPPF Medical Bulletin</i> 1975; 9(3): 3-4.4) Schiphorst LE, Collins WP, Royston JP. An estrogen test to determine the times of potential fertility in women. <i>Fertility and Sterility</i> 1985;44:328-334. <p>Although injectable progestins have no known teratogenic effects, avoiding the risk of fetal exposure is preferable on general principles. In addition, one study has suggested that <i>in utero</i> exposure may increase the risk of low birth weight babies.</p> <ol style="list-style-type: none">1) Simpson JL, Phillips OP. Spermicides, hormonal contraception and congenital malformations. <i>Advances in Contraception</i> 1990;6:141-147.2) Bracken MB. Oral contraceptives and congenital malformations in offspring: A review and meta-analysis of the prospective studies. <i>Obstetrics and Gynecology</i> 1990;76:552-557.

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Rationales

b) For a woman having menstrual cycles, no back-up method is needed if she is in the first 7 days of her menstrual cycle and is still menstruating. If she is in the first 7 days of her cycle, but is not menstruating, some programs may recommend use of a back-up method for 1 week. Injectables may be started anytime you can be reasonably sure the woman is not pregnant. However, if injections are started after day 7 of a regular cycle, a back-up method (or abstinence) may be needed (see c., below).

c) Although there is good reason to believe the effect on cervical mucus will promptly provide contraceptive protection within 24 hours, it may be prudent to consider a back-up method for up to 7 days.

(See Q.2. for postpartum initiation and Q.3. for post-abortion initiation.)

3) Pardthaisong T, Gray RH. In utero exposure to steroid contraceptives and outcome of pregnancy. *American Journal of Epidemiology* 1991;134(8):795-803.

b) It is probable that progestin-only injections effectively thicken cervical mucus within 24 hours. Consistent with this theory, progestin-only pills have been shown to produce a thickened mucus with low sperm penetration within 3 to 4 hours after pill ingestion. Natural progesterones also cause cervical mucus to become scant, thick and sticky, decreasing or inhibiting sperm penetration, usually within 24 hours, but sometimes within 48 hours. Clinical judgement is also consistent with this theory.

- 1) The Technical Guidance Working Group has reached this conclusion after a thorough review of the available literature and consultation with the following experts:
Gary Grubb, MD, MPH, The RW Johnson Pharmaceutical Research Institute, Raritan, NJ, USA
Michael Orme, Professor of Clinical Pharmacology, The University of Liverpool, UK.
- 2) Wright SW, Fotherby K, Fairweather F. Effect of daily small doses of Norgestrel on ovarian function. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970;77:65-68.
- 3) Tsibris JCM. Cervical mucus, in Gould JJ, Josimovich JB (eds). *Gynecologic Endocrinology*. New York, Plenum Medical Book Company, 1987, pp 175-183.
- 4) Insler V, Melmed H, Eichenbrenner I, Serr D, Lunenfeld B. The cervical score: A simple semiquantitative method for monitoring of the menstrual cycle. *International Journal of Gynaecology and Obstetrics* 1972;10(6):223-228.
- 5) Flynn AM, Lynch SS. Cervical mucus and identification of the fertile phase of the menstrual cycle. *British Journal of Obstetrics and Gynaecology* 1976(83):656-659.
- 6) Moghissi KS, Syner FN, Evans TN. A composite picture of the menstrual cycle. *American Journal of Obstetrics and Gynecology* 1972;114(3):405-418.

DMPA and NET-EN consistently inhibit ovulation.

- 1) *Injectable Contraceptives: Their Role in Family Planning Care*. Geneva, World Health Organization, 1990.
- 2) Mishell DR. Long-acting contraceptive steroids: Postcoital contraceptives and antiprogestins, in Mishell DR, Davajan V, Lobo RA, (eds). *Infertility, Contraception, and Reproductive Endocrinology*, 3rd edition. Boston, Blackwell Scientific Publications, 1991, pp 872-894.

c) Some programs might recommend a back-up method for women who are not menstruating at the time of progestin-only injectable initiation because there is a very slight risk of conception from unprotected intercourse on day 7 of the cycle.

Q.2. When can the first progestin-only injection be given postpartum?

Recommendations	Rationales
<p>For Breastfeeding Women:</p> <p>a) If the woman chooses to rely on the Lactational Amenorrhea Method (LAM), start injectable progestins when her menses* return, or when the woman is no longer fully or nearly fully breastfeeding or at 6 months postpartum, whichever comes first (see "Relying on Lactational Amenorrhea Method" in Definition).</p> <p>* NOTE: In breastfeeding women, bleeding in the first 56 days (8 weeks) postpartum is NOT considered "menstrual" bleeding, because it is not preceded by ovulation.</p>	<p>a) Risk of pregnancy during lactational amenorrhea is very low: less than 2% in first 6 months postpartum if fully breastfeeding; less than or equal to 7% in first 12 months. If the fully or nearly-fully breastfeeding woman remains amenorrheic, her risk of pregnancy is about the same as her risk with other modern contraceptive methods.</p> <ol style="list-style-type: none">1) Bellagio Consensus Conference on Lactational Infertility. Bellagio consensus statement on the use of breastfeeding as a family planning method. <i>Contraception</i> 1989;39(5):477-496.2) Kennedy KI, Visness CM. Contraceptive efficacy of lactational amenorrhea. <i>The Lancet</i> 1992;339:227-230.3) Perez A, Labbok MH, Queenan JT. Clinical study of the lactational amenorrhea method for family planning. <i>The Lancet</i> 1992;339:968-970.

Recommendations	Rationales
<p>b) If she does not want to rely on LAM, ideally wait at least 6 weeks postpartum to initiate injectable progestins.</p>	<p>b) Based on animal studies and observed fluctuations of human sex hormones in the first 6 weeks of life, plus the immaturity of the neonatal liver for the metabolism of exogenous steroids, it is considered prudent to wait to initiate progestin-only contraceptives until a breastfeeding woman is at least 6 weeks postpartum.</p>
<p>For Non-Breastfeeding Women:</p>	<ol style="list-style-type: none"> 1) Harlap S. Exposure to contraceptive hormones through breast milk - are there long-term health consequences? <i>International Journal of Gynaecology and Obstetrics</i> 1987;25(Suppl):47-55. 2) Ward RM. Pharmacologic principles and practicalities, in Taesch HW, Ballard RA, Avery ME (eds). <i>Diseases of the Newborn</i>. Philadelphia, WB Saunders Company, 1991. <p>Studies have detected no clinically measurable effects on the health or growth of breastfed babies of women who begin using progestin-only injectables at 6 weeks postpartum.</p> <ol style="list-style-type: none"> 1) WHO Task Force on Oral Contraceptives. Effects of hormonal contraceptives on milk volume and infant growth. <i>Contraception</i> 1984;30(6):505-521. 2) WHO Task Force on Oral Contraceptives. Special Programme of Research, Development, and Research Training in Human Reproduction. Effects of hormonal contraceptives on breast milk composition and infant growth. <i>Studies in Family Planning</i> 1988;19(6):361-369. 3) Karim M, Ammar R, El Mahgoub S, EL Ganzoury B, Fikri F, Abdou I. Injected progestogen and lactation. <i>British Medical Journal</i> 1971;1:200-203. 4) Pardthaisong T, Yencht C, Gray R. The long-term growth and development of children exposed to Depo-Provera during pregnancy or lactation. <i>Contraception</i> 1992;45:313-324. 5) Zacharias S, Aguilera E, Assenzo JR, Zanartu J. Effects of hormonal and non-hormonal contraceptives on lactation and incidence of pregnancy. <i>Contraception</i> 1986;33(3):203-213.
<p>a) The first progestin-only injection can be given immediately postpartum and whenever the service provider can be reasonably sure that the woman is not pregnant.</p>	<p>a) While there may be a theoretical concern of increased thrombogenic effect with COC use in the first week postpartum, there is no known clinical thrombogenic effect of progestin-only contraceptives; therefore injectable progestins can be safely used immediately postpartum, for non-breastfeeding women.</p> <ol style="list-style-type: none"> 1) <i>Injectable Contraceptives: Their Role in Family Planning Care</i>. Geneva, World Health Organization, 1990. 2) Fotherby K. The progestin-only pill and thrombosis. <i>The British Journal of Family Planning</i> 1989;15:83-85. 3) Chi I. The safety and efficacy of progestin-only oral contraceptives – An epidemiological perspective. <i>Contraception</i> 1993;47:1-21.

Q.3. Are progestin-only injectables appropriate for use immediately post-abortion?

Recommendations	Rationales
a) Yes, injectable progestins are appropriate for use immediately post-abortion (spontaneous or induced), in any trimester, and should be initiated within the first 7 days post-abortion (or anytime you can be reasonably sure the woman is not pregnant).	a) Fertility returns almost immediately post-abortion (spontaneous or induced): within 2 weeks for first trimester abortion and within 4 weeks for second trimester abortion. Within 6 weeks of abortion, 75% of women have ovulated. <ol style="list-style-type: none">1) Lähteenmaki P, Ylöstalo P, Sipinen S, Toivonen J, Ruusuvaara L, Pikkola P, Nilsson CG, Luukkainen T. Return of ovulation after abortion and after discontinuation of oral contraceptives. <i>Fertility and Sterility</i> 1980;34(3):246-249.2) Ostimihin BD, Otolorin ED, Ladipo OA. Sequential hormone measurements after first trimester abortion for normal Nigerian women. <i>Advances in Contraception</i> 1985;1 (1):83-90. <p>While there may be a theoretical concern of increased thrombogenic effect with COC use in the first week post-abortion, there is no known clinical thrombogenic effect of progestin-only contraceptives; therefore injectable progestins can be safely used immediately post-abortion (spontaneous or induced).</p> <ol style="list-style-type: none">1) <i>Injectable Contraceptives: Their Role in Family Planning Care</i>. Geneva, World Health Organization, 1990.2) Fotherby K. The progestin-only pill and thrombosis. <i>The British Journal of Family Planning</i> 1989;15:83-85.3) Chi I. The safety and efficacy of progestin-only oral contraceptives – An epidemiological perspective. <i>Contraception</i> 1993;47:1-21.

Q.4. Are there any age/parity restrictions on progestin-only injectables?

Recommendations	Rationales
<p>a) No. However, young and/or childless women in particular need to understand that, on average, it takes a woman four months longer to become pregnant after discontinuing DMPA than after discontinuing COCs, IUDs or barrier methods.</p>	<p>a) After discontinuing DMPA, about 50% of women conceive by 7 months (i.e., 10 months after the last injection). This time delay to conception is approximately 4 months longer than the time it takes for women who discontinue COCs, IUDs or barrier methods to conceive. Residual amounts of DMPA will remain in circulation for about 7 to 9 months after an injection, at which time serum levels of DMPA become undetectable. By about 2 to 3 years after discontinuation of DMPA, the proportion of women who have conceived is virtually the same as for those who have discontinued use of IUDs, diaphragms and COCs. The delay in return to fertility with NET-EN is presumed to be no more than with DMPA.</p> <ol style="list-style-type: none"> 1) Mishell DR. Long-acting contraceptive steroids: Postcoital contraceptives and antiprogestins, in Mishell DR, Davajan V, Lobo RA (eds). <i>Infertility, Contraception, and Reproductive Endocrinology</i>, 3rd edition. Boston, Blackwell Scientific Publications, 1991, pp 872-894. 2) <i>Injectable Contraceptives: Their Role in Family Planning Care</i>. Geneva, World Health Organization, 1990. 3) Schwallie PC, Assenzo JR. The effect of Depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: A review. <i>Contraception</i> 1974;10(4):181-202. 4) Pardthaisong T. Return of fertility after use of the injectable contraceptive Depo Provera: Up-dated data analysis. <i>Journal of Biosocial Science</i> 1984;16:23. 5) International Center for Medical Research Task Force on Hormonal Contraception. Return to fertility following discontinuation of an injectable contraceptive - NET-EN. <i>Contraception</i> 1986;34(6):573-582. 6) <i>Depo-Provera C-150 NDA 20-246</i>. Advisory Committee Brochure, 1992, p 37.

Recommendations	Rationales
<p>Older Women:</p> <p>b) Injectable progestins may be used by women through menopause. Risks for use of injectable progestins for older women appear minimal.</p>	<p>b) DMPA confers many non-contraceptive benefits including decreased menstrual blood loss, as well as protection against endometriosis, acute pelvic inflammatory disease (PID) and ectopic pregnancy and, of particular importance to older women, protection against endometrial cancer. DMPA may also inhibit intravascular sickling - an additional benefit to women who have sickle cell disease. Other effects which may be attributed to DMPA use include a slight increase in weight and slight (non-clinically significant) alterations in plasma lipid profiles. A theoretical risk of osteoporosis is currently under study.</p> <ol style="list-style-type: none"> 1) Depot-medroxyprogesterone acetate (DMPA) and cancer: Memorandum from a WHO Meeting. <i>Bulletin of the World Health Organization</i> 1986;64(3):375-382. 2) Liang AP, Levenson AG, Layde PM, Shelton JD, Hatcher RA, Potts M, Michelson MJ. Risk of breast, uterine corpus, and ovarian cancer in women receiving medroxyprogesterone injections. <i>Journal of the American Medical Association</i> 1983;249:2909-2912. 3) Kaunitz AM. Injectable contraception. <i>Clinical Obstetrics and Gynecology</i> 1989;32(2):356-368. 4) Shoupe D. Injectable contraceptives and contraceptive vaginal rings, in Shoupe D, Haseltine FP (eds). <i>Contraception</i>. New York, Springer-Verlag, 1993, pp 144-157. 5) Deslypere JP, Thiery M, Vermeulen A. Effect of long-term hormonal contraception on plasma lipids. <i>Contraception</i> 1985;31(3):633-642. 6) Oyelola OO. Fasting plasma lipids, lipoproteins and apolipoproteins in Nigerian women using combined oral and progestin-only injectable contraceptives. <i>Contraception</i> 1993;47:445-454. 7) Solheim F. An assessment of quality of life in women treated with Depo-Provera in Sweden, in Zambrano D (ed). <i>Depo-Provera® (medroxyprogesterone acetate) for Contraception: A Current Perspective of Scientific, Clinical & Social Issues</i>. Kalamazoo, Michigan, The Upjohn Company, 1992, pp 61-72. 8) De Ceulaer K, Gruber C, Hayes R, Serjeant GR. Medroxyprogesterone acetate and homozygous sickle cell disease. <i>Lancet</i> 1982;II:229-231. <p>Because women greater than 35 years of age are at increasing risk for endometrial (and ovarian) cancer, it is particularly important to:</p> <ul style="list-style-type: none"> ● carefully evaluate irregular bleeding before administering the injectable and ● more carefully consider cancer as a possible cause if the woman returns with irregular bleeding after prolonged amenorrhea. <ol style="list-style-type: none"> 1) Herbst AL, Mishell DR, Stenchever MA, Droegmueller W. <i>Comprehensive Gynecology</i>, 2nd edition. St. Louis, Mosby Year Book, 1992, pp 1082-1083.

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Adolescents:

c) Use of progestin-only injectables generally leads to amenorrhea (in 50% of women by the end of the first year and 66% by the end of the second year for DMPA). Some evidence suggests that a hypoestrogenic state (as evidenced by amenorrhea), within the first two years after menarche, may increase the risk of osteoporosis later in life, particularly for women with other risk factors for osteoporosis (e.g., women who are small-boned, underweight, white or Asian, smokers, or malnourished). However, for those adolescents age 15 and under, for whom progestin-only injectables are the most appropriate method, the benefits of the method generally outweigh the risks.

2) Parazzini F, La Vecchia C, Bocciolone L, Franceshi S. The epidemiology of endometrial cancer. *Gynecologic Oncology* 1991;41:1-16.

c) Amenorrhea while on progestin-only contraceptives is evidence of lower estrogen levels, and estrogen is necessary for the development and maintenance of strong bones (to prevent osteoporosis). The peak strength (density) of spinal bone is reached by girls around age 16; the greatest increase in bone density occurs in the first two years post-menarche.

- 1) Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. *Journal of Clinical Endocrinology and Metabolism* 1991;73:555-563.
- 2) Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, Bonjour JP. Longitudinal monitoring of bone mass accumulation in healthy adolescents: Evidence for a marked reduction after 16 years of age at The levels of lumbar spine and femoral neck in female subjects. *Journal of Clinical Endocrinology and Metabolism* 1992;75:1060-1065.
- 3) Dhuper S, Warren M, Brooks-Gunn J, Fox R. Effects of hormonal status on bone density in adolescent girls. *Journal of Clinical Endocrinology and Metabolism* 1990;71:1083-1088.

Q.5. What is the preferred site for a progestin-only injection?

Recommendations	Rationales
a) Both the arm (deltoid) and the gluteal muscle are acceptable. The choice should be made by client preference. The progestin-only injection is deep intra-muscular and should not be massaged.	a) The deltoid is generally more acceptable to the client and has easier access for service providers. 1) <i>Injectable Contraceptives: Their Role in Family Planning Care.</i> Geneva, World Health Organization, 1990. Some providers prefer to offer NET-EN in the gluteal muscle because the oil-based NET-EN requires a larger bore needle and may be painful. Massaging at the site of progestin-only injection increases immediate absorption. The objective of the depot formulation in oil is to achieve slow release over time.

Q.6. Is there a need for a rest period after a certain period of use of the progestin-only injectable, and is there a maximum recommended duration of use?

Recommendations	Rationales
a) No, there is no need for a rest period. Injectable progestins may be used for as long as a woman wishes to avoid pregnancy.	a) There is no cumulative effect of injectable progestins; the time required to clear the drug from the body is the same after multiple injections as after a single injection. 1) Mishell DR. Long-acting contraceptive steroids: Postcoital contraceptives and antiprogestins, in Mishell DR, Davajan V, Lobo RA (eds). <i>Infertility, Contraception, and Reproductive Endocrinology</i> , 3rd edition. Boston, Blackwell Scientific Publications, 1991, pp 872-894.

Q.7. Should the progestin-only injectable be discontinued because of extended amenorrhea?

Recommendations	Rationales
<p>a) No, there is no medical reason to discontinue. Emphasis should be on counseling, including reassurance that amenorrhea with injectable progestins is to be expected and is safe, as well as counseling on the benefits of amenorrhea.</p> <p>b) The question of whether progestin-only injectables may be related to osteoporosis is under study. In theory, this may be a particular concern for older women with prolonged amenorrhea. (See Q.4. concerning amenorrhea due to DMPA before age 16.)</p>	<p>a) It is reasonable to expect amenorrhea among injectable progestin users, and the likelihood of amenorrhea increases with increased duration of progestin-only injectable use (50% at end of first year, two-thirds of women by end of second year of use). Women who are counseled about this possible side-effect will be less concerned if they experience extended amenorrhea.</p> <p>1) Mishell DR. Long-acting contraceptive steroids: Postcoital contraceptives and antiprogestins, in Mishell DR, Davajan V, Lobo RA (eds). <i>Infertility, Contraception, and Reproductive Endocrinology</i>, 3rd edition. Boston, Blackwell Scientific Publications, 1991, pp 872-894.</p> <p>b) Extended amenorrhea resulting from the use of injectable progestins is due to endometrial atrophy. There is no risk of endometrial hyperplasia. In fact, DMPA is protective against endometrial cancer.</p> <p>1) Speroff L, Glass RH, Kase NG. <i>Clinical Gynecologic Endocrinology and Infertility</i>, 4th edition. Baltimore, Williams & Wilkins, 1989, p 201 and 227.</p> <p>2) Herbst AL, Mishell DR, Stenchever MA, Droegemueller W. <i>Comprehensive Gynecology</i>. St. Louis, Mosby-Year Book, 1992, pp 1082-1083.</p>

Q.8. How much grace period is there for subsequent progestin-only injections?

Recommendations	Rationales
<p>a) For DMPA (150 mg), on a 3-month schedule, it is acceptable to give the next injection:</p> <ul style="list-style-type: none"> ● up to 2 weeks late and possibly up to 4 weeks late depending on the population, or ● up to 4 weeks early though not ideal. <p>b) For NET-EN, on a 2-month schedule, it is acceptable to give the next injection:</p> <ul style="list-style-type: none"> ● up to 1 week late and possibly up to 2 weeks late depending on the population, or ● up to 2 weeks early though not ideal. 	<p>a) DMPA blood levels consistently remain high enough to maintain contraceptive effect through 3 months post-injection and the pregnancy risk at 4 months post-injection is extremely low (and DMPA has no known teratogenic effects, although one study has suggested <i>in utero</i> DMPA exposure may possibly increase risk of low birth weight babies).</p> <ol style="list-style-type: none"> 1) Mishell DR. Long-acting contraceptive steroids: Postcoital contraceptives and antiprogestins, in Mishell DR, Davajan V, Lobo RA (eds). <i>Infertility, Contraception, and Reproductive Endocrinology</i>, 3rd edition. Boston, Blackwell Scientific Publications, 1991, pp 872-894. 2) Bracken MB. Oral contraceptives and congenital malformations in offspring: A review and meta-analysis of the prospective studies. <i>Obstetrics and Gynecology</i> 1990;76:552-557. 3) Pardthaisong T, Gray RH. In utero exposure to steroid contraceptives and outcome of pregnancy. <i>American Journal of Epidemiology</i> 1991;134(8):795-803. 4) Schwallie PC, Assenzo JR. The effect of Depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: A review. <i>Contraception</i> 1974;10(4):181-202. <p>b) For NET-EN, blood levels remain high enough to maintain contraceptive effect through 74 days (2 months plus 2 weeks).</p> <ol style="list-style-type: none"> 1) Hall PE. Long-acting injectable formulations, in Diczfalusy E, Bygdeman M (eds). <i>Fertility, Regulation Today and Tomorrow</i>. New York, Raven Press, 1987, p 119.

Recommendations	Rationales
<p>c) If a client comes in after the grace period, advise her that delays in obtaining progestin-only injections increase the risk of pregnancy and <i>in utero</i> exposure to the progestin-only injectable. It is acceptable to give the progestin-only injection if you can be reasonably sure she is not pregnant. Although there is good reason to believe the effect on cervical mucus will promptly provide contraceptive protection within 24 hours, it may be prudent to consider a back-up method for up to 7 days. Reschedule the next injection (for 3 months with DMPA or 2 months with NET-EN).</p>	<p>c) It has been shown that the time it takes for progestin levels to be insufficient for contraception may vary somewhat from population to population. Studies show that Thai women seem to metabolize DMPA rapidly. Additionally, weight has also been shown to have an independent influence on progestin levels (in heavier women the contraceptive effects last longer).</p> <ol style="list-style-type: none">1) Garza-Flores J, Hall PE, Perez-Palacios G. Long-acting hormonal contraceptives for women. <i>Journal of Steroid Biochemistry and Molecular Biology</i> 1991;40(4-6):697-704.2) Fotherby K, Koetsawang S, Mathrubutham M. Pharmacokinetic study of different doses of Depo Provera. <i>Contraception</i> 1980;22(5):528-536.3) Bassol S, Garza-Flores J, Cravioto MC, Diaz-Sanchez V, Fotherby K, Lichtenberg R, Perez-Palacios G. Ovarian function following a single administration of Depo-medroxyprogesterone acetate (DMPA) at different doses. <i>Fertility and Sterility</i> 1984;42(2):216-222.4) World Health Organization. A multicentered phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: I. Contraceptive efficacy and side effects. <i>Contraception</i> 1986;34(3):223-235.

Q.9. If a woman complains of heavier menses and/or prolonged bleeding, is there a medical basis for discontinuing progestin-only injections?

Recommendations	Rationales
<p>Not usually. Irregular and prolonged bleeding episodes are common and expected in the first 3 to 6 months of use.</p> <p>a) For prolonged spotting or moderate bleeding (equivalent to normal menstruation but longer in duration), the first approach should be counseling and reassurance. It should be explained that in the absence of evidence for other diseases, irregular bleeding commonly occurs in the first few months of use of injectable progestins.</p> <p>If counseling and reassurance are not sufficient for the woman and she wishes to continue the method, the following management approaches may be tried:</p> <ul style="list-style-type: none"> ● short term (for 7 to 21 days) COCs or estrogen, or ● ibuprofen (or similar non-steroidal anti-inflammatories other than aspirin), or ● if the previous injection was given more than 4 weeks ago, giving another injection at this time may be an effective approach. <p>b) Heavy bleeding (greater than normal menstruation) is uncommon; it can usually be controlled by administration of increased doses of COCs (or estrogen). Some women will require stopping the use of injectable progestins due to medical reasons for</p>	<p>a) The number of bleeding days decreases with months of injectable progestin use.</p> <ol style="list-style-type: none"> 1) Belsey EM, Task Force on Long-Acting Systemic Agents for Fertility and Regulation. Menstrual bleeding patterns in untreated women and with long-acting methods of contraception. <i>Advances in Contraception</i> 1991;(7)257-270. <p>a-b) Management of prolonged or heavy bleeding may be achieved by:</p> <ul style="list-style-type: none"> ● rebuilding endometrium with COCs/estrogen, or ● ibuprofen* (which blocks prostaglandin synthesis and thus decreases uterine bleeding), or ● accelerating the arrival of amenorrhea with another injection. There is evidence that bleeding decreases with a subsequent injection. <ol style="list-style-type: none"> 1) <i>Injectable Contraceptives: Their Role in Family Planning Care</i>. Geneva, World Health Organization, 1990. 2) Diaz S, Croxatto HB, Davez M, Belhadj H, Stern J, Sivin I. Clinical assessment of treatments for prolonged bleeding in users of NORPLANT® Implants. <i>Contraception</i> 1990;42(1):97-109. 3) Task Force on Long-Acting Agents for the Regulation of Fertility. Multinational comparative clinical trials of long-acting injectable contraceptives: Norethisterone enanthate given in two dosage regimens and Depot-medroxyprogesterone acetate: Final report. <i>Contraception</i> 1983;28(1):1-20. <p>* NOTE: Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) should be used instead of aspirin because of aspirin's stronger and longer-lasting inhibitory effects on platelet aggregation (aspirin promotes bleeding).</p> <ol style="list-style-type: none"> 1) <i>American Hospital Formulary Service Drug Information</i>. Bethesda, MD, American Society of Hospital Pharmacists, 1994, p 1208.

Recommendations	Rationales
<p>excessive bleeding or due to the client's preference.</p> <p>c) If suspected, abnormal conditions which cause prolonged or heavy bleeding should be evaluated and treated as appropriate.</p> <p>d) Some prolonged or heavy bleeding may fail to be corrected and injections may need to be discontinued.</p> <p>e) Evaluate and address anemia if indicated. Give nutritional advice on the need to increase the intake of iron-containing foods.</p> <p>f) Do not perform uterine evacuation unless another medical condition is suspected (vacuum aspiration is generally the preferred method of uterine evacuation).</p>	<p>2) Field CS. Dysfunctional uterine bleeding. <i>Primary Care</i> 1988;15(3):561-574.</p>

Q.10. Is an early second injection effective for controlling heavy bleeding?

Recommendations	Rationale
<p>It is not known. There is no clear evidence that a second depo- medroxyprogesterone acetate (DMPA) injection (given 4 to 12 weeks after the first injection) offers measurable benefits for controlling heavy bleeding, but the existing studies are inadequate to address the question.</p>	<p>One study found a decrease in the number of days of bleeding and/or spotting in women immediately following each re-injection every 12 weeks.</p> <p>Another study found no significant difference in the bleeding patterns of adolescents re-injected at 6 weeks compared to those re-injected at 12 weeks.</p> <p>However, there were several limitations to the studies and more research is needed.</p> <ol style="list-style-type: none">1) WHO Special Programme of Research, Development and Research Training in Human Reproduction. Multinational comparative clinical trial of long-acting injectable contraceptives: norethisterone enanthate given in two dosage regimens and depot-medroxyprogesterone acetate. Final Report. <i>Contraception</i> 1983;28(1):1-21.2) Harel Z, Biro FM, Kollar LM. Depo Provera in adolescents: effects of early second injection or prior oral contraception. <i>Journal of Adolescent Health</i> 1995;16:379-84.

Q.11. Can progestin-only injectables be safely initiated and resupplied only by doctors?

Recommendations	Rationales
a) No. Injectable progestins (including immediate postpartum injection in non-lactating women and post-abortion injection) can be safely administered by service providers (e.g., nurses, midwives, pharmacists, community-based distribution (CBD) workers, and others) who are appropriately trained according to relevant national or institutional standards.	a) Nurses, midwives, and other community health workers can be appropriately trained to initiate and resupply injectable progestins. 1) <i>Injectable Contraceptives: Their Role in Family Planning Care.</i> Geneva, World Health Organization, 1990.

Q.12. Should progestin-only injectables be provided if infection prevention measures cannot be followed?

Recommendations	Rationales
<p>a) No.</p> <p>All sites providing progestin-only injectable contraceptives should consistently follow basic infection prevention measures, including:</p> <ul style="list-style-type: none"> ● aseptic technique (including cleaning of the progestin-only injection site); ● sterile needles and syringes (single use, disposable needles/syringes are preferred); ● if sterilization of reusable needles/syringes is impossible, decontamination with bleach followed by high-level disinfection — if correctly executed — may be used; and ● safe disposal of single-use needles/syringes. 	<p>a) Because injecting a steroid contraceptive, such as Depo Provera[®], penetrates the protective skin barrier, careful aseptic technique must be followed to prevent infection. One type of infection associated with this procedure is an injection abscess, commonly caused by normal skin flora (staph and strep). Thorough skin preparation done before the progestin-only injection will remove most microorganisms from the client's skin which helps prevent cellulitis (skin infection) and abscess formation at the injection site.</p> <p>Another concern is the increasing problem of transmission of hepatitis B and AIDS viruses to clients, health care providers and clinic staff, especially cleaning and housekeeping personnel. To minimize this risk, whenever possible, single-use (disposable) needles and syringes should be used. If reusable needles and syringes are used, they should be decontaminated immediately after use by soaking in 0.5% chlorine solution or other locally available and approved disinfectant. These practices, when combined with the proper disposal of single-use needles and syringes, protect clinic staff, especially cleaning and housekeeping personnel, from contracting hepatitis B or AIDS following accidental needlesticks. Following decontamination, reusable needles and syringes should be thoroughly cleaned and finally sterilized or high-level disinfected.</p> <p>1) Tietjen L, Cronin W, McIntosh N. <i>Infection Prevention for Family Planning Service Programs: A Problem-Solving Reference Manual</i>. Durant, OK, Essential Medical Information Systems, Inc., 1992, p 181.</p>

Classification of Selected Procedures for Progestin-Only Injectables (DMPA and NET-EN)

Procedure	Class	Rationale
Pelvic examination (speculum and bimanual)	C	<ul style="list-style-type: none"> • Conditions which would restrict use of injectables should be identified by history before method initiation. • A pelvic exam may reveal reproductive tract infections or reproductive tract malignancies which should be treated for optimal preventive care. Routine pelvic exam screening for asymptomatic women, in the absence of tests for cervical cancer, however, is a low yield procedure¹. • In some cases, a pelvic exam may help evaluate the question of pregnancy beyond 6 weeks duration: in this case it is Class A. • A pelvic exam is not necessary to ensure safe use of injectables as a contraceptive method.
Blood pressure	C	<ul style="list-style-type: none"> • Screening for high blood pressure is part of optimal preventive health care. • Current evidence does not demonstrate any notable effect of DMPA or NET-EN on blood pressure^{2,3}.
Breast examination	C	<ul style="list-style-type: none"> • For all women of reproductive age or beyond, a breast exam is recommended for optimal preventive health care. • Injectables do not cause breast cancer⁴. Lumps that are suspicious for cancer should be evaluated. While any hormonal treatment may in theory cause such lumps to grow, pregnancy causes much higher hormonal levels; therefore, potential malignancies of the breast should not be a reason to delay a woman's access to the use of this contraceptive method.
Sexually transmitted disease (STD) screening by lab tests (for asymptomatic persons)	C	For optimal health care, clients at risk for STDs (by personal history or socio-demographic risk factors) should be offered STD screening where possible. However, presence of an STD will not affect the safe use of injectables.

Procedure	Class	Rationale
Cervical cancer screening	C	<ul style="list-style-type: none"> ● Cervical cancer screening is indicated for women at risk of cervical carcinoma, and is recommended for optimal preventive health care for women of reproductive age or beyond (particularly women at risk of STDs). <p>NOTE: Cervical cancer screening is advised for optimal preventive care for all women at risk of cervical cancer (e.g., smokers, women with partners having multiple partners, women with young age at first intercourse, etc.). All women at risk should ideally have access to a practical method of cervical cancer screening, treatment and follow up.</p> <ul style="list-style-type: none"> ● Cervical screening is not needed for the safe use of injectables⁵.
Routine, mandatory lab tests (e.g., cholesterol, glucose, liver function tests)	D	The effects of injectables on cholesterol, blood glucose and normal liver function are slight, and of no demonstrated clinical significance ⁶ .
General counseling points for progestin-only injectables use: <ul style="list-style-type: none"> ● efficacy ● common side effects ● correct use of method ● signs and symptoms for which to return to the clinic ● STD protection (when/as appropriate) 	A	<ul style="list-style-type: none"> ● Accurate client education is essential for maximum quality of family planning services. ● Appropriate counseling about common contraceptive side effects at the time of method selection can lead to improved client satisfaction and contraceptive continuation⁷.
Counseling concerning change in menses, including irregular or absent menstrual bleeding	A	Irregular or absent menstrual bleeding is the single most common side effect of progestin-only injectables, and the chief complaint leading to discontinuation ^{2,3} .

KEY:

- Class A** = essential and mandatory or otherwise important in all circumstances, for safe and effective use of the contraceptive method
- Class B** = medically/epidemiologically rational in some circumstances to optimize the safe and effective use of the contraceptive method, but may not be appropriate for all clients in all settings
- Class C** = may be appropriate for good preventive health care, but not materially related to safe and effective use of the contraceptive method
- Class D** = not materially related to either good routine preventive health care or to the safe and effective use of the contraceptive method

Citations:

- 1) Huber DH, Huber SC. Screening oral contraceptive candidates and inconsequential pelvic examinations. *Studies in Family Planning* 1975;6(2):49-51.
- 2) WHO Special Programme of Research, Development and Research Training in Human Reproduction. Multinational comparative trial of long-acting injectable contraceptives: Norethisterone enanthate given in two dosage regimens and depot-medroxyprogesterone acetate: Final report. *Contraception* 1983;28(1):1-20.
- 3) WHO Task Force on Long-Acting Systemic Agents for Fertility Regulation, Special Programme of Research, Development and Research Training in Human Reproduction. A multi-centered phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: I. Contraceptive efficacy and side effects. *Contraception* 1986;34(3):1223-1235.
- 4) *Injectable Contraceptives: Their Role in Family Planning Care*. Geneva, World Health Organization, 1990, p 69.
- 5) The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. *Contraception* 1992;45:199-312.
- 6) *Injectable Contraceptives: Their Role in Family Planning Care*. Geneva, World Health Organization, 1990, p 78.
- 7) Cotten N, Standback J, Maidouka H, Taylor-Thomas JT, Turk T. Early discontinuation of contraceptive use in Niger and The Gambia. *International Family Planning Perspectives* 1992;18(4):145-149.