Effects of Injectable or Implantable Progestin-Only Contraceptives on Insulin-Glucose Metabolism and Diabetes Risk

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Progestin-only contraceptives administered by injection (Depo-Provera) or subcutaneous implant (Norplant) have been available to U.S. women for about a decade. Two epidemiological studies found their use associated with increased incidence of type 2 diabetes. In reviewing publications relating progestin injections and implants to glucose metabolism, 25 studies of various study designs and laboratory methods were identified that reported at least one insulin value in nondiabetic women. Research subjects were usually nonobese and often from developing countries. Of eight studies that performed sequential oral glucose tolerance tests (OGTTs) after at least 6 months of Depo-Provera or Norplant use, seven found significant elevations (approximate doubling) of insulin at 2 or 3 h after glucose challenge; the effects on fasting, half-hour, or 1-h postchallenge insulin values were less consistent. The three studies that performed sequential intravenous glucose tolerance tests (IVGTTs) on injection users all found an increased early-phase insulin response. One study used sequential hyperglycemic-hyperinsulinemic clamps to demonstrate reduced total-body glucose uptake per unit of insulin after 8 weeks of Norplant use. The metabolic studies generally did not show a reduction in the glucose tolerance of their nondiabetic subjects. However, compared with the lean and low-risk women who were usually selected for metabolic research, many U.S. women receiving these injections or implants may start out with increased insulin resistance due to greater weight, sedentary lifestyle, and family or childbearing histories. Additional research could help clarify whether exposure to injectable or implantable contraceptives leads to increased risk of type 2 diabetes and gestational diabetes in women with predisposing factors.

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In the early 1990s two new modes of progestin-only hormonal contraception became available to women living in the U.S. The following decade has been notable for the emergence of type 2 diabetes among adolescent girls (more than boys) (1) and a rising prevalence of gestational diabetes (2). The temporal overlap of a diabetes increase among young women and availability of new contraceptive methods has stimulated us to review the published literature on insulin-glucose metabolism in the presence of these hormonal agents.

One new contraceptive mode was a depot injection containing 150 mg medroxyprogesterone acetate (DMPA, "Depo-Provera"). Administered by the intramuscular route, it delivers medroxyprogesterone at a plasma concentration of ~1 ng/ml (3). The DMPA injection must be repeated every 3 months for continuing contraceptive benefit. The other new mode was a system of six Silastic capsules, each containing 36 mg of the progestin levonorgestrel (LNG), designed for long-term subcutaneous insertion in the upper arm (LNG implant, "Norplant"). This implant system delivers LNG initially at ~85 μg/day, declining gradually to ~30 μg/day (4). Serum concentrations of LNG decrease from ~0.35 ng/ml at 1 year to ~0.29 ng/ml at 5 years, the recommended duration of use.

Both of these new contraceptives are highly effective (≤0.3% pregnancies with typical use in the first year [5]) and require relatively little active involvement from the patient. In addition, the absence of any estrogenic hormone component makes them theoretically attractive for use by diabetic women who are at advanced risk of vascular complications. For diabetic women free of microvascular or macrovascular disease, the World Health Organization (WHO) acknowledges that progestin-only contraceptives in general (i.e., progestin-only pills as well as injections and implants) may slightly influence carbohydrate metabolism, but the WHO also indicates that the advantages of DMPA or LNG implants generally outweigh their theoretical or proven risks (6). The WHO's favorable review of the LNG implants extends also to diabetic women with vascular disease, but for these women it considers DMPA to carry theoretical or proven risks that usually outweigh the advantages.

The American College of Obstetricians and Gynecologists has stated that among diabetic women who have vascular disease or are older than 35 years, the

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Abbreviations: DMPA, depot injection of medroxyprogesterone acetate (Depo-Provera); IUD, nonhormonal intrauterine device; IVGTT, intravenous glucose tolerance test; LNG, levonorgestrel; NET-EN, norethisterone enanthate; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

use of progestin-only oral contraceptives, DMPA, or implants may be safer than combination (i.e., estrogen plus progestin) oral contraceptives (7). It adds, however, that "because of its long duration of action and potential for hypoestrogenic effects, DMPA may be less appropriate than other progestin-only contraceptives." The American Diabetes Association offers little contraceptive guidance for diabetic women beyond commenting that "There are no contraceptive methods that are specifically contraindicated in women with diabetes (8)."

For nondiabetic women with previous gestational diabetes, the WHO indicates "no restriction" for the use of injectable or implantable methods (6). On the other hand, experts at the Fourth International Workshop-Conference on Gestational Diabetes Mellitus cautioned that progestin-only contraception should be avoided, if possible, until more data are available on their safety in women with prior gestational diabetes (9).

Literature search

This review began with a MEDLINE search for articles on humans published since 1980 that mentioned both contraceptive progestins and an aspect of insulin-glucose metabolism. This search identified 309 citations of which only one article (10) was about an injectable contraceptive and also included a topic related to epidemiology, risk, or odds ratio. In addition, a large prospective cohort study was informally identified that related an implantable contraceptive to many health outcomes, including diabetes (11).

Pertinent metabolic studies were sought by retrieving all articles among the 309 citations for which the keywords or abstracts indicated there might be data reported on at least one insulin value in association with injection or implant use. From these articles, additional bibliographic citations were identified that preceded 1980 or were otherwise missed in the MEDLINE search. After consolidation of multiple reports from the same research program, 15 metabolic studies were found that reported insulin values among nondiabetic women using various progestin-only injections (Table 1) and 10 among nondiabetic women using various progestin-only implants (Table 2). In addition, one study was found of diabetic and prediabetic women who had insulin measurements in connection with their DMPA use (12).

Two epidemiological studies

One epidemiological study was a case-control study of Navajo women that found DMPA contraception was associated with a greater risk of diabetes than alternative contraceptives (10). Diabetic case subjects ($n = 284$) were age-matched to nondiabetic control subjects ($n = 570$). Records were reviewed to determine contraceptive use before the date of diabetes diagnosis. This study population was obese with a mean BMI of 30.6 kg/m^2 and a 6% prevalence of prior gestational diabetes among the nondiabetic control subjects. The diabetic case subjects had a mean BMI of 38.3 kg/m^2 and a 38% prevalence of prior gestational diabetes. Previous users of DMPA were more likely to be diabetic cases than women who had used only combination estrogen-progestin oral contraception (odds ratio [OR] 3.8 [95% CI 1.8–7.9]). The excess risk persisted after adjustment for BMI (3.6 [1.6–7.9]). Users of DMPA were also more likely to be diabetic cases than women who had never used hormonal contraception, although excess risk was smaller (2.4 [1.4–3.6]). Longer use was associated with greater risk of diabetes.

In the other epidemiological study, a cohort of LNG implant initiators ($n = 7,977$) was prospectively compared with age-matched, nonhormonal intrauterine device (IUD) initiators ($n = 6,625$) and sterilization users ($n = 1,419$) (11). Participants came from eight developing countries and were relatively lean (mean weight ~55 kg [SD 11]). Compared with the group using IUDs or sterilization, the implant current users had a nonsignificantly increased incidence of diabetes after adjustment for clinic, age, and body weight (relative risk [RR] 2.4 [95% CI 0.7–8.1]). The incidence of diabetes in this young, lean group was 0.2 per 1,000 woman-years of LNG implant use.

Metabolic studies in nondiabetic women

The 15 studies of injectable contraceptives listed in Table 1 include reports with a variety of study designs, sample sizes, laboratory methods, and progestin formulations. The most common design was a time series of contraceptive users, usually without a comparison group or randomization of contraceptive method. Loss to follow-up was generally not addressed. Of the six DMPA studies with insulin values that followed healthy contraceptive users at least 6 months with sequential oral glucose tolerance tests (OGTTs), all showed a significant elevation of insulin concentration (compared with baseline before DMPA) at 2–3 h after the glucose challenge (13–18). The increase in these late postchallenge insulin values was typically about double, but the variation in assay methods and the absence of normative standards make it difficult to interpret these increments. The effects of DMPA on fasting, half-hour, or 1-h postchallenge insulin measurements were varied and inconsistent.

For users of injectable norethisterone enanthate (NET-EN, not currently available in the U.S.), a similar elevation in late postchallenge insulin values was found in one study (18) but not in another (19). Studies of either DMPA or NET-EN that evaluated patients by intravenous glucose tolerance test (IVGTT) all showed increased early-phase insulin responses with injectable contraceptive use (20–22).

Despite the effects noted on insulin values, most of the studies in Table 1 did not find any effect of the injectable contraceptives on glucose concentrations in lean, glucose-tolerant women. Studies that found increased glucose involved DMPA users who were heavier at baseline (mean weight ≥68 kg) (13,18) or had longer duration of use (at least 48 months) (16).

Of the 10 metabolic studies of progestin implants used by nondiabetic women (Table 2), 7 involved LNG users, and the others involved implantable progestins not currently available in the U.S. (nestorone, nomegestrol, and etonogestrel). Only two studies evaluated LNG users by repeated OGTT after at least 12 months. The first of these reported an increase in the insulin area under the curve along with a doubling of 3-h insulin values (23,24). The investigators also described a decline in postchallenge insulin concentrations at 4 weeks after removal of the LNG implant, but the insulin area under the curve remained greater than it had been before the implant (25). The second study showed a similar increase in the insulin area under the curve but only a nonsignificant increase in the 2-h insulin

Table 1—*Metabolic studies of women using injectable progestin-only contraceptives with outcomes related to insulin*

First author, year, site (ref. no.)	Formulations tested (*n* women)	Description of women, protocol	Effects on insulin (I)	Effects on glucose (G)
DMPA				
Spellacy, 1972 Florida, U.S. (13)	150 mg IM q 3 months (37)	68 ± 17 kg Tested baseline and 12 months by 3-h OGTT	↑ I at 0 h* and 0.5 h† and 1 h, 2 h*, and 3 h‡ Change in mean I at 3 h of 30→57 μU/ml	↑ G at 0 and 0.5 h‡ at 1 and 2 h*, and at 3 h†. Of 29 "normal" at baseline, 17 became borderline and 1 became abnormal
Vermeulen, 1974, Belgium (14)	150 mg IM q 3 months (20)	Within 10% of ideal body weight Tested baseline, 4 and 7 months by 2-h OGTT	↑ I at 0.5 h† and 2 h* Change in mean I at 3 h of 18→39 μU/ml	↑ G at 0 h†
Tuttle, 1974, Ottawa, Canada (15)	400 mg IM q 6 months, continuous users for 12–30 months (18) Control group >6 months without hormone therapy (14)	11 users and 7 controls were potential diabetics based on family or childbearing history 65 ± 3 kg (DMPA); 57 ± 7 kg (control) Two groups compared by 3-h OGTT	↑ I at 0 h‡ and 3 h†	No mean differences between users and control subjects However, a 20-year-old overweight user became diabetic after 13 months
Tankeyoon, 1976, Bangkok, Thailand (20)	150 mg IM q 3 months 16; 13 tested after 9 months and 15 after 12 months	Tested baseline, 1, 9, and 12 months by IVGTT	↑ I response within 30 min of IV glucose after 9 and 12 months No change in fasting I	↑ rate of G disappearance ('k') after 1*, 9, and 12 months. ↓ fasting G after 12 months*
Dhall, 1977, Chandighar, India (63)	150 mg IM given only once (13)	Hostel residents tested at baseline, 3 weeks and 12 weeks by 1-h OGTT (50-g load)	No changes	No changes
Amatayakul, 1980, Chiang Mai, Thailand (21)	150 mg IM q 3 months (12)	Tested baseline 3, 6, and 12 months by IVGTT	↑ first-phase I response‡. No change in fasting I	No change in fasting G or G disappearance
Amatayakul, 1985, Chiang Mai, Thailand (22)	150 mg IM q 3 months (10)	Tested baseline, 1, 6, 14, 27, and 52 weeks, then 6 months after removal by IVGTT	↑ I during treatment at 0 min, 10 min†, and 20 min§; all returned to baseline values after removal	No change in G values or G disappearance
Liew, 1985, Singapore (16)	Continuous IM users (q 3–6 months) for 6–84 months (157) Control group not on steroid hormones (162)	56 ± 9 kg (DMPA); 53 ± 9 kg (controls) No family history of diabetes or large babies Two groups compared by 3-h OGTT	DMPA users had ↓ I at 0.5 h‖, but ↑ I at 2.5 h†	DMPA users had ↑ G† (AUC), esp at 0.5 h‡ and 2.5 h* ↑ G (AUC) by 15%† for long-duration users (48+ months)

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Table 1—*Continued.*

First author, year, site (ref. no.)	Formulations tested (*n* women)	Description of women, protocol	Effects on insulin (I)	Effects on glucose (G)
Virutamasen, 1986, Bangkok, Thailand (17)	>5 years of continuous IM use (57) Control group not on steroid hormones (24)	0–65 kg tested by 3-h OGTT for users (just prior to DMPA injection) and controls (in follicular phase)	DMPA users had ↑ I at 1–3 h†. Mean I at 3 h was 23.6 for users and 8.5 for controls† (units not stated)	Four DMPA users had abnormal glucose tolerance, of whom three returned to normal after discontinuation.
Fahmy, 1991, Cairo, Egypt (18)	150 mg IM q 3 months (20) Not on steroid hormones (18 to 10)	69 ± 10 kg No liver disease Tested baseline, 3, 6, and 12 months by 2-h OGTT blood test	↑ I at 0 h after 6 months* and 12 months‡; ↑ I at 2 h after 6 and 12 months No significant differences after glucose challenge	↑ G at 0, 0.5, 1, 1.5, and 2 h after 12 months
NET-EN				
Dhall, 1977 Chandighar, India (63)	200 mg IM given only once (11)	Hostel residents Tested at baseline, 3 weeks and 12 weeks by 1-h OGTT (50-g load)	No changes	No changes
Andino, 1981 Havana, Cuba (64)	200 mg IM given only once (8)	Tested baseline and in 2nd month by 3-h OGTT	↓ I at 1 h†; ↑ I at 2 h‡	No change in G
Amatayakul, 1985 Chiang Mai, Thailand (22)	200 mg IM q 8 weeks for 6 months, then once 12 weeks later (9)	Tested baseline, 1, 6, 14, 25, and 50 weeks, then 6 months after removal by IVGTT	↑ I during treatment at 0 min*, 20 min†, 40 min, 60 min*, 90 min§; all except 0-min values returned to baseline values after removal	No change in fasting G or G disappearance
Griffin, 1988 London (19)	200 mg IM continuously for 5–8 years (31) Control group not on steroid hormones (18)	BMI 25 ± 5 (NET-EN) BMI 24 ± 4 (control) Tested by fasting blood test	Fasting test: ↑ I, ↑ I/G ratio OGTT: ↑ I/G ratio at 0 h, but no significant differences after glucose challenge	No differences in G
Fahmy, 1991, Cairo, Egypt (18)	200 mg IM q 2 months for 6 months, then q 84 d for 6 months (20)	69 ± 10 kg No liver disease Tested baseline 3, 6, and 12 months by 2-h OGTT	↑ I at 0 h after 6 months‡, returned to baseline after 12 months, ↑ I at 2 h after 3, 6, and 12 months‡	↑ G at 0, 0.5, 1, 1.5, and 2 h after 6 months; G returned to baseline levels after 12 months

All participating women were explicitly or implicitly free of diagnosed diabetes and not recently pregnant. *$P < 0.01$; †$P < 0.05$; ‡$P < 0.001$; §$P < 0.02$; ‖$P < 0.0002$. AUC, area under the curve; IM, intramuscular injection; IV, intravenous; q, every.

Table 2—*Metabolic studies of women using implantable progestin-only contraceptives with outcomes related to insulin*

First author, year, site (ref. no.)	Formulations tested (*n*, women)	Description of women, protocol	Effects on insulin (I)	Effects on glucose (G)
LNG implant				
Lithell, 1983, Sweden (65)	LNG implant (5)	67 ± 12 kg Tested baseline and following removal after 6–13 months by IVGTT and fasting insulin	↑ fasting I (8 → 12 μU/ml) (unclear significance). No data on post-challenge insulin	No change in IVGTT
Konje, 1992, Ibadan, Nigeria (23, 24)	Norplant (20 followed 18 months and 13 followed 30 months)	57 ± 9 kg Tested baseline, 1 month and q 6 months after insertion by 3-h OGTT	↑ I (AUC) by 38% in 1 month then 45–51% for months 6–30 For 12th months change in mean I at 3 h 43→107 μU/ml*	↑ G (AUC) by 12% in 1 month, 27% in 6 months and 39%–42% for months 12–30 For 12th month change in mean G at 2 h 3.9 → 5.6 mmol/l*
Konje, 1992, Ibadan, Nigeria (25)	Norplant (24); removal after 18–30 months	57 kg Tested baseline, before removal, and 4 weeks after removal by 3-h OGTT	↓ I after removal, remaining above baseline levels at 2, 2.5, and 3 h† After removal I (AUC) was greater than baseline*	G returned close to baseline levels ($P = 0.16$) after removal
Shamma, 1995, Connecticut, U.S. (27)	Norplant (7)	Within 20% ideal body weight Tested baseline and 8 weeks after implant by hyperglycemic-hyperinsulinemic clamp	↑ first-phase I response by 37%‡, ↑ second-phase I response by 48%§ ↓ steady-state M:I by 17%‖ No change in fasting I	↑ M by 18%‡ No change in fasting G
Koopersmith, 1995, California, U.S. (66)	Norplant (10)	Tested baseline and 12 weeks after implant by insulin tolerance test	No change in fasting I or in fractional disappearance rate for I	No change in fasting G or in fractional disappearance rate for G
Harper, 1997, North Carolina, U.S. (42)	Norplant (9)	68 kg (50–91 kg) Tested baseline and 6 months by FSIGT	No change in insulin sensitivity by Bergman minimal model	↑ G at 0 h ($P \sim 0.05$)
Biswas, 2001, Singapore (26)	Norplant (40; 36 followed through 12 months, 31 through 24 months)	Tested baseline, 6, 12, and 24 months by 2-h OGTT	↑ I (incremental AUC) by 72% after 24 months† For 24th month, change in mean I at 0 h 44→60 pmol/1†, at 2 h 364→556 pmol/l (NS)	↑ G (incremental AUC) by 92% after 24 months ($P < 0.05$) For 24th month, change in mean G at 2 h 5.6→6.6 mmol/l (NS) No change in HbA_{1c}
Nestorone (ST-1435) implant				
Odlind, 1984, Uppsala, Sweden (67)	ST-1435 implant (5)	64 ± 9 kg Tested baseline, 1, 6 months by 2-h OGTT	↑ mean I at 2 h (21→30→26 μU/l) (NS), influenced by one subject who gained weight.	No change

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values (26). Both of these studies identified an increase in glucose (area under the curve) that appeared to increase with greater duration of LNG implant use.

In a study of LNG implant users evaluated at baseline and 8 weeks after insertion by hyperglycemic clamp, investigators found increased first- and second-phase insulin responses along with a small increase in total-body glucose uptake; the steady-state rate of glucose uptake per unit of plasma insulin signifi-

Table 2—*Continued.*

First author, year, site (ref. no.)	Formulations tested (*n*, women)	Description of women, protocol	Effects on insulin (I)	Effects on glucose (G)
Nomegestrol implant				
Barbosa, 1995, Bahia, Brazil (68)	Uniplant, implant with 55 mg nomegestrol (18; 15 followed for 2 years)	55 ± 6 kg Tested baseline, 1, 3, 6, 12, 18 and 24 months by fasting venous blood sample	No change in fasting I	No change in fasting G, HbA_{1c}
Etonogestrel implant				
Biswas, 2001, Singapore (26)	Implanon, implant with 68 mg etonogestrel (40; 39 followed through 12 months, 37 through 24 months)	Tested baseline, 6, 12, and 24 months by 2-h OGTT	↑ I (incremental AUC) by 54% after 24 months For 24th month, change in mean I at 0 h 51→73 pmol/l†, at 2 h 336→584 pmol/l†	↑ G (incremental AUC) by 49% after 24 months For 24th month, change in mean G at 2 h 5.4→6.1 mmol/l†, change in mean HbA_{1C} 4.2→4.4 %†

All participating women were explicitly or implicitly free of diagnosed diabetes and not recently pregnant. *$P < 0.0001$; †$P < 0.05$; ‡$P = 0.003$; §$P < 0.001$; ‖$P = 0.03$. AUC, area under the curve; FSIGT, frequently sampled intravenous glucose tolerance test; q, every.

cantly declined, indicating decreased tissue sensitivity to insulin (27).

Metabolic studies in prediabetic women and diabetic patients

A small study of potentially diabetic women (having a history of abnormal glucose tolerance during pregnancy and a newborn infant weighing >9 lbs) evaluated its four participants by repeat OGTT (12). After 1–2 months of DMPA exposure, there was an increase in 1-h and 2-h insulin response to the glucose challenge. After 3–12 months of continuing DMPA use insulin returned to pretreatment levels, whereas 1-h and 2-h glucose concentrations continued to increase. The authors interpreted these observations as showing that the DMPA increased the need for insulin but that, with time, the potentially diabetic women could no longer compensate for this additional insulin requirement.

This same report also described the administration of DMPA to eight patients with frank type 2 diabetes (including five males) who were evaluated by OGTT at baseline and after 1–3 months of DMPA use at two different doses (12). These eight diabetic patients ranged in age from 27 to 62 years, and none of them was treated with hypoglycemic drugs or insulin. For these patients the insulin values at 0.5 and 1 h after glucose challenge declined within 1–3 months after starting DMPA treatment, while their glucose values increased. In the view of the authors, the β-cells of these patients could not respond, even transiently, to the increased need for insulin induced by DMPA.

For women using contraceptive implants, no studies were found that measured insulin or C-peptide in prediabetic or diabetic patients.

DISCUSSION

Trends in use prevalence of injectable or implantable contraceptives

Data on use prevalence of injectable and implantable contraceptives are necessary to assess any potential public health impact on diabetes risk. In the U.S., use prevalence of these contraceptive methods has generally been low. In 1995, among all U.S. women aged 15–44 years, 1.9% were using injectables and 0.9% were using implants (28). Use prevalence of injectables was slightly higher among younger women: 2.9% among those aged 15–19 years and 3.9% for those aged 20–24 years. With regard to implants, use prevalence was also higher among women aged 20–24 years (2.4%), but not for those aged 15–19 years (0.8%). Approximately half of injectable users and 16% of implant users discontinued use within 12 months (29). Non-Hispanic black women had the highest use prevalence (3.3% for injectables and 1.4% for implants), followed by Hispanic (2.8 and 1.2%, respectively), and Caucasian (1.6 and 0.7%, respectively) women. In some Native American communities, e.g., Navajo (10), use prevalence of injectables is also relatively high.

In the absence of annual, national contraception surveys, trends in use prevalence can be inferred only from limited marketing information or from experience in specific populations. Norplant was approved for the U.S. in 1990, and its use increased until the mid-1990s when the prevalence began to drop as the media focused on its side effects (30). As of August 2000, Norplant System kits for insertion were no longer available in the U.S. (31). DMPA was approved as a contraceptive for the U.S. in 1992 but was used off label as a contraceptive method before its approval (32). The most comprehensive trend data come from the federally funded Title X program, which serves almost 4,000,000 primarily low-income contraceptive users per year in the U.S.

These data show an increase in the use of injectables from 12% among contraceptive users in 1995 to 19% in 2000 and a decline in implant users from 2% in 1995 to 0% in 2000 (33). Data from the King County Family Planning Program in Washington state also show an increasing trend in injectable use from 2.7% of contraceptive users in 1992 to 16.6% in 1999 (34).

Given the low use prevalence of implantable and injectable contraceptives among the general population of U.S. women, these contraceptive methods are not likely to have contributed much to the general increase in diabetes incidence over the last decade. However, their possible impact must be considered in specific populations where use prevalence has been relatively high. For example, among U.S. women aged 15–19 years who used any contraceptive in 1995, 19% of non-Hispanic blacks were using injectables compared with only 8% of Caucasians (35). Among adolescents attending a clinic in Baltimore in 1992–1993, 29% chose implants (36). High use prevalence has also been reported among postpartum teens: 50% chose injectables in one study (37) and 48% chose implants in another (38). Another study of postpartum adolescents reported that 43% of African-American, 33% of Mexican-American, and 24% of Caucasian women chose DMPA (39).

Possible mechanisms relating injectable and implantable contraceptives to diabetes risk

The elevations observed in late postchallenge insulin concentrations among nondiabetic injection and implant users (Tables 1 and 2) may reflect compensation for increased insulin resistance. This presumption of increased insulin resistance is supported by a finding of increased free fatty acids after glucose challenge among DMPA users (15). Increased free fatty acids are associated with insulin-resistant states (40) and glucose intolerance (41). Similarly, LNG implant users have been shown to have reduced total-body glucose uptake per unit of insulin (27).

On the other hand, a study using Bergman minimal-model analysis found no change in insulin sensitivity among women who accepted an LNG implant (42). Thus, the increases observed in postchallenge insulin values may be related to a mechanism other than increased insulin resistance. A direct stimulation of pancreatic β-cells is conceivable, consistent with metabolic studies showing an increased early-phase insulin response. Primary stimulation of early insulin production, however, would be inconsistent with the epidemiological observation of increased diabetes incidence among these women. Furthermore, the acute insulin response usually declines rather than rises, as patients progress to impaired glucose tolerance and diabetes (43).

Other possible explanations for the increase in peripheral insulin include diminished clearance, less degradation, or increased return to the circulation of cell-associated insulin in an immunoreactive form (44). It is also conceivable that the insulin assays used by earlier investigators were indiscriminately detecting elevations of proinsulin. If this were the case, concerns about an increase in diabetes risk would still be appropriate. Increased levels of peripheral proinsulin are associated with reduced acute insulin response, a defect in insulin secretion, and eventual progression to type 2 diabetes (45). Future studies using better laboratory methods could help to clarify the physiological pathways leading to postchallenge hyperinsulinemia.

If indeed the use of injectable or implantable contraceptives leads to increased insulin resistance among some women, the mechanisms underlying this effect remain to be elucidated. One general mechanism that could tie injectable or implantable contraceptives to insulin resistance is promotion of weight gain. Cross-sectional and longitudinal studies of DMPA users have generally found increased mean weight (46–48) that appears to be associated with changes in adipose mass rather than fluid or lean tissue (49). Among DMPA users attending urban clinics in Texas, weight gain was the most commonly reported side effect, mentioned by 38–46% of recipients at each follow-up contact (50).

Women using LNG implants also tend to gain weight. Among implant users followed in four U.S. academic medical centers, weight gain during 5 years averaged ~1 kg per year (51), a larger increase than the mean of ~0.3 kg per year typical of U.S. women in a similar age range (52). The large 5-year study in eight developing countries reported that implant users experienced more weight gain (RR 6.9 [95% CI 4.6–10.5]) but also more weight loss (2.6 [1.5–4.7]) (11). For continuing implant users in this international study, the average 5-year weight change was +2.5 kg (SE 0.07) in contrast to +1.5 kg (0.08) for the comparison group ($P < 0.001$).

Another general mechanism leading to increased insulin resistance could be related to the simulation of a chronically pregnant state by the exogenous progestin. Among older women, a history of multiple pregnancies is associated with increased insulin values and decreased insulin sensitivity, an association that is independent of obesity and fat distribution (53). High parity may also be associated with glucose intolerance (54) and a modestly increased risk of dying from diabetes (55). Among women with previous gestational diabetes, the occurrence of another pregnancy approximately triples the risk of type 2 diabetes after adjustment for multiple other diabetes risk factors (56). Oral progestin-only contraceptives (analogous to injections and implants) may similarly mimic the pregnant state. The use of oral, progestin-only contraceptives among women with previous gestational diabetes almost triples the risk of type 2 diabetes compared with the use of low-dose combination oral contraceptives or nonhormonal contraceptives (57).

These associations between the pregnant state and diabetes risk highlight the long-term disease-reduction benefits of providing contraceptive opportunities for women who desire to avoid pregnancy. At the same time, these associations raise concern that some contraceptive modes might themselves increase disease risk through their simulation of pregnancy or by other mechanisms (e.g., increases in adipose tissue) that contribute to insulin resistance.

Implications in an era of increasing diabetes

Published metabolic studies have generally found no association between women's use of injectable or implantable progestin-only contraceptives and the development of glucose intolerance. However, recent epidemiological reports suggest a possible increased risk of diabetes among users of DMPA (10) or LNG implants (11). Resolution of this apparent discrepancy may have to consider the increased insulin response among women who adopt these contraceptive injections or implants.

The high insulin concentration of women using progestin-only contraceptives is likely evidence of their increased insulin resistance. The subjects of the published metabolic research were generally lean, so their compensatory hyperinsulinemia was probably sufficient to preserve their glucose tolerance. However, women who are heavier or insulin resistant for other reasons would be less able to respond with complete pancreatic compensation. Thus, injection or implant users with this predisposition might proceed more readily into glucose intolerance.

U.S. women of the 1990s probably had more insulin resistance than the research subjects in whom injectable and implantable contraceptives were first evaluated in earlier decades. The increased insulin resistance of the more recent period was likely associated with women's greater obesity (58) and more sedentary practices. Among U.S. female adolescents surveyed in 1996, participation in moderate to vigorous physical activity decreased substantially with age; young women who were non-Hispanic blacks or Hispanics (the groups most likely to adopt contraceptive injections or implants) had lower levels of physical activity than women of other racial or ethnic groups (59).

The overall use prevalence in the U.S. of injections and implants appears to have risen during the early 1990s and has since leveled off (DMPA) or declined (LNG implants). However, DMPA or LNG implants may have been preferentially prescribed for U.S. women with prior gestational diabetes or a diabetic family history when their physicians were concerned about vascular disease risk associated with estrogen-containing contraceptives. This recommendation of progestin-only contraceptives in the context of increased insulin resistance in the population may possibly help to explain the recent emergence of type 2 diabetes in some young women (1). Similarly, among women who became pregnant following discontinuation of a progestin injection or implant, a comparable synergism may have contributed to an increase in gestational diabetes (2). Interestingly, the recent rise in gestational diabetes in northern California leveled off after about 1997, a time course that roughly follows the popularity in use of injectable and implantable contraceptives.

Any conclusions about a possible link between contraceptive method and the incidence of diabetes remain speculative and hypothetical. Regardless of how well the time trends associated with diabetes incidence and use of contraceptive injections and implants might (or might not) fit together, any parallel trends could be entirely unrelated. An analysis that compares groups rather than individuals is susceptible to ecological bias (where the effects based on the comparison of groups fail to reflect the biologic effects at an individual level), problems with control of extraneous variables, and temporal ambiguity, e.g., lack of certainty that contraceptive use preceded diabetes (60). Analytic studies that include information on the joint distribution of both exposure (use of contraceptives) and outcome (incident diabetes) in individual women are needed to explore the biologic effects.

It is beyond the scope of this review to specify the contraceptive methods that might be optimal for women who are known to be insulin resistant or frankly diabetic. A comprehensive recommendation would have to consider not only the contraceptives' effects on insulin and glucose but also other risk variables for chronic disease (e.g., lipids, blood pressure, coagulation factors, liver function) (61), weight changes, and major clinical end points. Toward this end, Diab and Zaki (62) have recently reported prospective experience among diabetic women with hormonal contraceptives (DMPA, LNG implants, and low-dose combination oral contraceptives) and compared numerous chemical changes with those in diabetic women who used copper IUDs. However, their clinical study was small (fewer than 20 women using each of the contraceptive modes) and their participants were primarily women with type 1 diabetes. Expanded clinical studies of this sort, especially with women having type 2 diabetes, would be very useful. Future research and clinical surveillance are needed to clarify appropriate contraceptives for prediabetic and diabetic women and to determine whether contraceptive injections or implants may have a role in increasing the risk of diabetes.

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