Safety of implantable contraceptives for women: data from observational studies

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Authors' objectives
To review the findings from observational studies on the safety of contraceptive implants.

Searching
MEDLINE and POPLINE were searched up to April 2001. In addition, the reference lists from reviews and other key articles were handsearched. The search was limited to English language publications in peer-reviewed journals.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were randomised controlled trials (RCTs) where the results were reported for the entire study sample, cohort studies, case-control studies and cross-sectional studies. Non-comparative trials and non-randomised pre-marketing trials, in which the participants chose the contraceptive method, were also included.

Specific interventions included in the review
The inclusion criteria were contraceptive implants including Norplant (levonorgestrel), Jadelle (levonorgestrel), the Chinese equivalents of Norplant and Jadelle, Implanon (etonogestrel), Surplant/Uniplant (nomegestrol) and Elcometrine (nestorone).

Participants included in the review
The inclusion criteria were not explicitly stated. The participants included in the review were women using a contraceptive implant and comparison groups of women using other methods of contraception (e.g. sterilisation).

Outcomes assessed in the review
The inclusion criteria were death, neoplastic disease, cardiovascular events, hypertension, changes in bone density, gall bladder disease, diabetes, serious mental disorders, anemia, thrombocytopenia, pelvic inflammatory disease (PID), human immunodeficiency virus or acquire immunodeficiency syndrome (HIV/AIDS) and connective tissue disorders. The outcomes in the review also included surrogate outcomes such as changes in blood-pressure or haemoglobin levels and the discontinuation rates for specific health outcomes.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The author did not state that they assessed validity, except to classify all evidence as level II on a hierarchy of evidence. The authors did not state how this classification was performed.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included the study design, the outcome of interest, the numbers of participants in the intervention and control groups, the nature of the control group if one was included, and the length of follow-up. For each study, the relative risks (RRs) were calculated for each outcome where this was possible.

Methods of synthesis
How were the studies combined?
A narrative synthesis of studies that reported on the health outcomes specified in the inclusion criteria was undertaken;
details of these studies were also tabulated.

**How were differences between studies investigated?**

The studies reporting on the clinical outcomes specified in the inclusion criteria were discussed separately on the basis of outcome reported. Studies that reported on surrogate markers were not included in the narrative synthesis or the table of study details.

**Results of the review**

Fifty-five studies were included in the review, of which 17 reported on the occurrence of health outcomes specified in the inclusion criteria.

There were 3 reports on the overall rates of adverse events, of which 2 were meta-analyses. The incidence of adverse events in implant users was low and was not significantly different to the expected rate(s) in control groups.

The mortality rates of implant users were low and did not differ from the expected rate among women of reproductive age or among women using other methods of contraception.

No studies with sufficient numbers of participants or length of follow-up, to adequately assess the risk of neoplastic disease in implant users, were found.

Cardiovascular events were rare among Norplant users, although there was no evidence to assess whether the rates differed from those women not using hormonal contraception.

Most studies examining mean blood-pressure measurements in implant users over time did not show significant differences over time. However, a large cohort study found a significant difference in the incidence of hypertension or borderline hypertension between Norplant users and intra-uterine device (IUD) users, with the RR greater for Norplant users (RR 1.81, 95% confidence interval, CI: 1.12, 2.92).

There was no association between the use of contraceptive implants and decreases in bone mineral density.

A large cohort study found that the incidence of gall bladder disease in current users of Norplant, IUDs and sterilisation were 1.5, 1.3 and 1.0 per 1,000 woman-years, respectively. The difference between the Norplant users and controls was not significant when current use was examined (RR 1.31, 95% CI: 0.87, 1.96), but it became significant when the initial contraceptive method was examined (RR 1.52, 95% CI: 1.02, 2.27).

In a 5-year cohort study, 8 Norplant users (0.2 per 1000 woman-years) and 3 controls developed diabetes giving a non significantly higher rate among Norplant users (RR 2.42, 95% CI: 0.73, 8.05).

The only study to examine serious mental disorders showed no difference between Norplant users and controls not using hormonal contraception (RR 1.72, 95% CI: 0.58, 5.13).

The use of contraceptive implants was not associated with decreased levels of haemoglobin or increased rates of anaemia.

A large cohort study reported 3 cases of thrombocytopenia among Norplant users with none among non-users. The rate among Norplant users was 9 per 100,000 woman-years, which was comparable to US background rates of 2.6 to 7.4 per 100,000 woman-years.

A large cohort study found that there was a lower incidence of both acute PID (RR 0.34, 95% CI: 0.14, 0.85) and unspecified PID (RR 0.54, 95% CI: 0.39, 0.74) among Norplant users than among women with IUDs or sterilised women. When Norplant users were compared only with women who had been sterilised, there was no difference in the rates of acute or unspecified PID.

No evidence was found on changes in the risk of HIV transmission or disease progression in HIV-positive women in contraceptive implant users.
One large cohort study found no association between the incidence of the connective tissue disorders systemic lupus erythematosus and systemic sclerosis and the use of Norplant. It also found a non significantly increased risk of rheumatoid arthritis in Norplant users (RR 3.46, 95% CI: 0.72, 16.6), based on 9 cases.

**Authors' conclusions**
The use of contraceptive implants is safe. Women using implants do not experience adverse events at higher rates than non-users.

**CRD commentary**
The review question was not explicitly stated, although the inclusion criteria were reasonably clear. This may have increased the likelihood that subjective decisions would be made when selecting the studies for the review. In addition, the author did not report using methods to minimise error and bias when selecting the studies and extracting the data for the review. Two relevant electronic databases were searched, but since the search was limited to studies published in English this may have led to the introduction of language bias. The restriction of the review to published studies may also have led to the introduction of publication bias.

The review included a large number of studies that employed surrogate markers for health outcomes, but these were excluded from both the narrative synthesis and the table of study details. This table did not show fully the results of all 17 included studies with clinical outcomes. The focus on clinical outcomes increased the relevance of the conclusions, which were appropriately cautious, to the review question. However, the decision to limit the review (with noted exceptions) to observational studies may mean that these conclusions do not fully reflect the available evidence.

**Implications of the review for practice and research**
The author did not state any implications for practice or further research.

**Bibliographic details**

**PubMedID**
11861058

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Bone Density /drug effects; Cohort Studies; Contraceptive Agents, Female /adverse effects; Controlled Clinical Trials as Topic; Diabetes Mellitus /chemically induced; Drug Implants; Female; Gallbladder Diseases /chemically induced; HIV Infections /chemically induced; Hematologic Diseases /chemically induced; Humans; Hypertension /chemically induced; Mortality; Neoplasms /chemically induced; Neurocognitive Disorders /chemically induced; Pelvic Inflammatory Disease /chemically induced

**AccessionNumber**
12002000667

**Date bibliographic record published**
30/06/2004

**Date abstract record published**
30/06/2004
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.