Ectopic pregnancy with use of progestin-only injectables and contraceptive implants: a systematic review

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Abstract

Background: Use of contraception lowers a woman’s risk of experiencing an ectopic pregnancy. In the case of method failure, however, progestin-only contraceptives may be more likely to result in ectopic pregnancies than some other methods such as combined hormonal and barrier contraceptives.

Objective: To describe ectopic pregnancy risk associated with use of implants and progestin-only injectable contraceptives through a systematic review of published studies.

Data Sources: We searched electronic databases for articles in any language published through May 2015 describing studies of progestin-only injectables and implants. We also searched bibliographies and review articles for additional studies.

Study Selection and Extraction: Studies that reported any pregnancies were included in the review. Independent data extraction was performed by two authors based on predefined data fields, and where possible, we calculated the proportion of pregnancies that were ectopic and the ectopic pregnancy incidence rate per 1000 woman–years.

Results: Fifty-three studies of implants and 28 studies of injectables were identified; 79% reported pregnancy location. The proportion of ectopic pregnancy ranged from 0 to 100% with an incidence of 0–2.9 per 1000 woman–years in studies of marketed levonorgestrel implants. Studies of etonogestrel implants and the injectables, depot-medroxyprogesterone acetate and norethisterone enanthate, reported few ectopic pregnancies.

Conclusion: Progestin-only contraceptive implants and injectables protect against ectopic pregnancy by being highly effective in preventing pregnancy overall; however, the absolute risk of ectopic pregnancy varies by type of progestin. Risk of ectopic pregnancy should not be a deterrent for use or provision of these methods.

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Keywords: Contraception; Ectopic pregnancy; Progestins; Implants; Injectables

1. Introduction

1.1. Rationale

Ectopic pregnancies are an important cause of maternal morbidity and mortality worldwide. In the United States and other developed countries, an estimated 1–2% of all pregnancies are ectopic [1–3], accounting for 3–5% of pregnancy-related deaths [4,5]. In less developed regions, data on ectopic pregnancy are sparse; however, case fatality is considerably higher [6–9].

Risk factors for ectopic pregnancy include, but are not limited to, age, history of pelvic inflammatory disease (PID), smoking, infertility, in vitro fertilization and prior ectopic pregnancy [3,10,11]. An estimated half of ectopic pregnancies appear to be caused by delay in transport of a fertilized ovum to the uterus due to the damage of the fallopian tubes caused by infection or surgery [12]. It has also been hypothesized that low levels of progestin seen with some progestin-only contraceptive methods, while failing to inhibit ovulation, may impact tubal motility and increase the risk of a pregnancy being ectopic [13]. The labels for the levonorgestrel (LNG)-containing contraceptive implant Jadelle® and the etonogestrel (ENG)-containing implant Implanon® (and its successor, Nexplanon®) warn that...
although the methods lower a woman’s absolute risk of ectopic pregnancy because they lower the probability of pregnancy, in the case of contraceptive failure, the implants may be associated with an increase in the relative proportion of pregnancies that are ectopic [14,15].

Women who experience method failure after female tubal sterilization or while using hormonal or nonhormonal intrauterine device (IUDs) or progestin-only pills (POPs) have been reported to have a higher relative risk of ectopic pregnancy than users of combined oral contraceptives (COCs) or condoms [16–19]. A review of clinical data submitted to the Food and Drug Administration for marketing approval of contraceptives found that the proportion of pregnancies that were ectopic ranged from 0 out of 27 among users of COCs, to 1 out of 21 among POP users, to 1 out of 2 among users of the LNG IUD [20].

Several published reviews of ectopic pregnancy risk with the use of sterilization, IUDs, POPs and emergency contraceptive pills (ECPs) have been conducted [13,21–24]; however, no thorough assessment of the association between progestin-only implants or injectables and ectopic pregnancy has been published. Understanding whether and how ectopic pregnancy risk varies by these methods is important for both women and providers, especially since common side-effects associated with these methods, including irregular bleeding and lower abdominal pain, can also be signs of ectopic pregnancy.

1.2. Objective

The objective of this review is to describe the risk of ectopic pregnancy among users of progestin-only injectables and contraceptive implants based on a comprehensive review of published research.

2. Methods

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [25].

2.1. Eligibility criteria

This review includes all published studies that presented pregnancy data with use of any contraceptive implant (marketed or not) and any progestin-only injectable. We included both comparative analyses as well as single-arm observational studies; however, studies that only presented pregnancy data for subgroups of women (such as those on hepatic-enzyme inducers or those participating in clinical trials of HIV prevention drugs) were excluded. We also excluded case reports and review articles, although relevant studies from review articles were collected and evaluated for inclusion.

2.2. Search strategy and data extraction

We searched for studies of contraceptive implants or injectables in any language that included pregnancy as an outcome using the electronic databases MEDLINE (via PubMed), POPLINE, LILACS and EMBASE published through May 2015 (search terms listed in Appendix A). We also hand searched reference lists and review articles for relevant studies.

Two authors (RC, IY) independently reviewed the search results for studies potentially eligible for inclusion. Articles considered potentially relevant and published in a language other than English were translated by native speakers of the particular language. Two authors (RC, IY) independently read full-text articles to determine eligibility for inclusion, that is, they presented data on pregnancy. For articles where pregnancy site — intrauterine or ectopic — was not reported, we contacted the authors via email to request this information. After the list of eligible studies was established, two authors (RC, IY) independently extracted data from the studies using an extraction table developed for the purpose. Extracted data included study design, length of follow-up, contraceptive regimen(s), number of women–months and women–years of exposure, number of pregnancies and number of ectopic pregnancies. For articles in which the number of women–years was not reported, it was calculated by dividing the number of reported women–months by 12. The proportion of pregnancies that were ectopic and ectopic pregnancy incidence rate per 1000 woman–years was then calculated for each regimen included in the study. After data extraction was complete, the two authors compared results and resolved any discrepancies.

2.3. Risk of bias in individual studies

While the aim of this review is to describe the risk of ectopic pregnancy with use of progestin-only injectables and implants, we do not present a summary estimate of risk for these methods given the wide variation in research design, outcome measures and study populations. We employed a comprehensive search strategy designed to capture all relevant studies in order to qualitatively describe risk. Given our broad inclusion criteria, we did not attempt to assess data quality or the risk of bias for all included studies. However, we do report study design and size for each included study in Appendices B1 and B2.

3. Results

Our search produced 884 potentially relevant articles, of which 81 met the eligibility criteria described above (Fig. 1). We found 53 studies of progestin contraceptive implants [26–78] and 28 studies of progestin-only injectables [79–106] reporting any pregnancies. Most of the studies were prospective cohort (n=41) or nonrandomized comparative (n=16) studies; however, 18 were randomized trials, five were chart reviews and one was a review of regulatory agency surveillance data (Table 1).

3.1. Implants

The implant studies included seven different progestins and a wide variety of regimens (Table 2). Some studies included multiple progestins and multiple regimens. By far, the most
commonly studied progestin was LNG, with most data coming from studies of the six-rod 5-year implant system, Norplant®, \((n=28)\) containing 216 mg of LNG. For 50 of the 53 implant studies, location of pregnancy was either reported in the publication or was obtained through correspondence with the study authors. Forty-six studies reported woman–months or woman–years of exposure allowing for calculation of ectopic pregnancy incidence.

### 3.1.1. Implants studied but not marketed

In general, studies of older nonmarketed implants reported higher incidence of ectopic pregnancy (Table 2). For example, the ectopic pregnancy incidence rate among women using a single silastic capsule containing 47 mg of norgestrienone for 6 months was 51.8 per 1000 woman–years [57]. Women who were implanted with five 30-mg capsules of megestrol acetate (MA) and used them for approximately 1 year had an ectopic pregnancy incidence rate of 41.6 per 1000 woman–years [61]. The high pregnancy and ectopic pregnancy rates observed with some of these early implants were important reasons why these products never reached the market.

Among five studies of Norplant II, the predecessor to the two-rod LNG-releasing implant Jadelle, that included site of implantation, one reported an ectopic pregnancy at 15 months of use in a woman with a history of ectopic pregnancy [42] resulting in an ectopic pregnancy rate of 2.6 per 1000 woman–years.

### 3.1.2. Marketed implants

Twenty-eight studies of Norplant are included in the review, 25 of which reported site of implantation. Among those 25, 14 (56%) reported no ectopic pregnancies. The ectopic pregnancy incidence rate among the other 11 ranged from 0.1 to 2.9 per 1000 woman–years, and the proportion of pregnancies that were ectopic ranged from 3.1% to 100% (Table 2). The highest ectopic incidence rate was reported in a study of 208 Norplant users (345 woman–years) in New York City [37]. In that study, an intrauterine pregnancy at month 14 and an ectopic pregnancy at month 24 occurred in women weighing more than 175 lb. Only one other early study of Norplant reported an ectopic incidence of more than 2.0 [45]. In that study, only two pregnancies occurred; however, both were ectopic. The remaining nine studies reported rates under 1.0 ectopic pregnancies per 1000 W-Y.

Though fewer in number, studies of other marketed LNG-containing implants including Jadelle (150 mg), Sino-implant (216 mg) and Sino-implant (II) (150 mg) reported somewhat similar rates of ectopic pregnancy as the Norplant studies. Two studies of Jadelle included ectopic pregnancies,

### Table 1

Number of published studies of progestin-only implant and injectable contraceptives reporting any pregnancies by study design.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Implants ((N=53))</th>
<th>Injectables ((N=28))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial(^a)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Nonrandomized comparative cohort study(^b)</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Prospective cohort study(^c)</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Chart review(^d)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Regulatory agency surveillance data(^e)</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) [34,42,47,53,65,71,75,77,79,81,86,87,95,96,100,102–104].

\(^b\) [33,35,38,51,56–58,61,62,64,74,76,83,94,105,106].

\(^c\) [26–32,36,37,39,40,44–46,48–50,52,54,55,59,60,63,66,67,69,70,72,73,78,84,85,89–91,93,97–99,101].

\(^d\) [41,43,80,82,92].

\(^e\) [68].
one during the fifth year of use resulting in a rate of 0.5 per 1000
woman–years [47] and one at 84 months of use (incidence rate
could not be calculated) [78]. Two large randomized trials of
Sino-implant (II) did not report pregnancy location; however,
correspondence with authors indicated that all pregnancies were
intrauterine [75, 77]. Postmarketing surveillance studies of
Sino-implant (II) in Kenya and Pakistan following 754
women reported a single ectopic pregnancy out of five
pregnancies occurring within the first year of use resulting in
an ectopic pregnancy rate of 0.8 per 1000 woman–years [69].

Pregnancy incidence in studies of the single-rod Implanon/
Nexplanon (containing 68 mg of ENG) is even lower, with most
studies reporting zero pregnancies. We found only two studies
of Implanon that reported any pregnancies, one with no ectopic
pregnancies [76] and one reporting five [68]. The latter study
was a review of surveillance data submitted to Australia’s drug
regulatory agency, which included 218 unintended pregnancies
associated with Implanon use. Only 13 of those pregnancies
were believed to be true method failures, and it is not clear if the
five ectopic pregnancies were among that group. Exposure time
was also not captured in these data, so we could not calculate an
ectopic pregnancy incidence rate.

3.1.3. Dose effect

Data on the effect of progestin dose on ectopic pregnancy risk
are limited; however, a couple of studies provide some evidence.
In a study in which women received 90- or 120-mg LNG
implants, an ectopic pregnancy incidence rate of 8.3 per 1000
women–years was observed for the two groups combined [62],
which is considerably higher than even the highest rates observed
in studies of Norplant or Jadelle, which contain 216 and 150 mg
of LNG, respectively. This may be because lower dose implants
have a lower daily release rate and thus are less effective in
preventing pregnancy, including ectopic pregnancy. An early
study comparing silastic and ethylene vinyl acetate (EVA)
rod release rates ranging from 10 to 40 mcg/day resulted in
three pregnancies, including one ectopic, among
women using a single silastic rod releasing 10 or 20 mcg/day [64].

3.2. Injectables

Two types of progestin-only injectables are included in this
review, depot-medroxyprogesterone acetate (DMPA) and
norethisterone enanthate (NET-EN), in several different dosages
(Table 3). Many injectable studies did not report pregnancy
location. After contacting study authors, we obtained

Table 2
Proportion of pregnancies that were ectopic and ectopic pregnancy incidence by implant type and regimen among studies for which pregnancy location is
known.a

<table>
<thead>
<tr>
<th>Progestin (dosage)</th>
<th>No. of</th>
<th>No. of</th>
<th>No. of studies reporting any ectopic pregnancies</th>
<th>% of pregnancies that were ectopicc</th>
<th>Ectopic pregnancy incidence per 1000 w-yc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever-marketed regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Norplant (6 silastic rods, 216 mg) [26–50]</td>
<td>25</td>
<td>61432</td>
<td>11</td>
<td>3.1–100</td>
<td>0.1–2.9</td>
</tr>
<tr>
<td>Jadelle (2 silastic rods, 150 mg) [46,47,78]</td>
<td>3</td>
<td>11391</td>
<td>2</td>
<td>20–33</td>
<td>0.4, d</td>
</tr>
<tr>
<td>Sino-implant (I) (6 silastic rods, 216 mg) [33,34,65,75,77]</td>
<td>5</td>
<td>22399</td>
<td>1</td>
<td>25</td>
<td>0.8</td>
</tr>
<tr>
<td>Sino-implant (II) (2 silastic rods, 150 mg) [34,65–67,69,70,75,77]</td>
<td>8</td>
<td>25425</td>
<td>3</td>
<td>8.3–20</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>ENG</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Implanon/Nexplanon (single EVA rod, 68 mg) [68,76]</td>
<td>2</td>
<td>205654</td>
<td>1</td>
<td>2.3</td>
<td>d</td>
</tr>
<tr>
<td>Regimens studied but never marketed</td>
<td></td>
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<tr>
<td>LNG</td>
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<tr>
<td>Norplant II Covered Rods (2 silastic rods, 140 mg) [38,42,54,55,72]</td>
<td>5</td>
<td>3023</td>
<td>1</td>
<td>16.7</td>
<td>2.6</td>
</tr>
<tr>
<td>3–6 silastic capsules (30 mg each) [62,71]</td>
<td>2</td>
<td>657</td>
<td>1</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>3-keto-desogestrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single silastic implants (10, 20, 40 mcg/day) [64]</td>
<td>1</td>
<td>33</td>
<td>1</td>
<td>50</td>
<td>179.2</td>
</tr>
<tr>
<td>Single ENG implants (15 &amp; 30 mcg/day) [64]</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MA</td>
<td></td>
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<td></td>
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<tr>
<td>4–6 silastic capsules (23–30 mg each) [56,61,62]</td>
<td>3</td>
<td>825</td>
<td>2</td>
<td>7.1–66.7</td>
<td>11.4–41.6</td>
</tr>
<tr>
<td>4 MA+1 or 2 LNG silastic capsules (20–30 mg each) [62]</td>
<td>1</td>
<td>244</td>
<td>1</td>
<td>8</td>
<td>3.7</td>
</tr>
<tr>
<td>Norgestrieneone</td>
<td></td>
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<tr>
<td>1–6 silastic capsules (30–47 mg each) [57,63,71]</td>
<td>3</td>
<td>1131</td>
<td>2</td>
<td>6.2–11.1</td>
<td>4.5–51.8</td>
</tr>
<tr>
<td>Norethisterone (NES)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>3–5 silastic capsules or 1 silastic rod (35mg each) [59]</td>
<td>1</td>
<td>282</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nomegestrol acetate</td>
<td></td>
<td></td>
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<tr>
<td>Uniplan (1 silastic rod, 55 mg) [60]</td>
<td>1</td>
<td>1803</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Norethindrone (NET)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5 silastic capsules or 1 silastic rod (20–40 mg each) [62,74]</td>
<td>2</td>
<td>199</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Site of implantation could not be determined for 3 studies.
b Some studies contained more than one progestin and/or regimen.
c Among studies that reported any ectopic pregnancies.
d Exposure time not reported.
Pregnancy rates in the 27 studies of injectable contraceptives were low. Among 10 studies of DMPA for which the pregnancy rate was reported or could be calculated, rates ranged from 0.1 to 1.7 per 100 woman–years [83,87,89,96–98,103–106]. Among studies of NET-EN, rates ranged from 0.3 to 6.6 per 100 woman–years [79,81,83,88,90,91,93,96,101–103]. Only three studies — two of NET-EN and one of DMPA — reported any ectopic pregnancies. The two associated with NET-EN use occurred in studies of nonmarketed regimens: monthly administration of 20 mg [93] and 200 mg given every 74 or 80 days [85]. In the former study, the duration of use and the time of the ectopic pregnancy were not reported. In the latter, a total of four pregnancies were documented with one being ectopic, and the ectopic pregnancy rate was 3.4 per 1000 woman–years. The ectopic pregnancy occurred approximately 40 days after the second injection in a woman with a history of PID. Finally, four ectopic pregnancies were reported among 949,182 users of 150-mg im DMPA in a review of Planned Parenthood Federation of America insurance data collected between 1994 and 1998 [82]. The pregnancy data from this review are incomplete, however, as site of implantation is only documented for 37% of clients between 1997 and 1998 compared to almost 98% of clients between 1994 and 1995, and the review does not report when the four ectopic pregnancies occurred. We did not find any studies of the subcutaneous formulation of DMPA reporting ectopic pregnancy.

### 4. Discussion

Contraceptive methods such as LNG or ENG-containing implants are highly effective; in a Cochrane review, no pregnancies were reported in either the Implanon or Norplant groups after 26,972 and 28,108 woman–months of follow up, respectively [107]. Among women not using contraception, 1–2% of pregnancies are ectopic. Studies of progestin-only implants described in this review report higher proportions of ectopic pregnancies in the event pregnancy occurs; however, our review confirms that the absolute risk of ectopic pregnancy is lower for women using these methods compared with noncontraceptors. The large, multicountry, postmarketing study of Norplant offers a good example of this lowered risk. Investigators found an ectopic pregnancy incidence rate of 0.3 per 1000 woman–years among Norplant users compared with a rate of 2.66 among women not using contraception. The ectopic pregnancy incidence rate was even higher (9.24 per 1000 woman–years) in a subgroup of women not using contraception who were planning pregnancy [35]. In the present review, the highest incidence of ectopic pregnancy reported among marketed implants was 2.9 per 1000 woman–years, which is close to that estimated for noncontracepting women (2.1 per 1000 woman–years [108]); most studies, however, reported incidence below 1.0 per 1000 woman–years.

The only other progestin used in currently marketed implants (Implanon/Nexplanon) is ENG. Only three studies of implants containing this progestin report any pregnancies; two of these studies were with the marketed product Implanon including a review of postmarketing surveillance data. While five of the 218 pregnancies reported in that review were ectopic, because of data limitations, it is unknown how many of them occurred among women who had the device in situ [68]. The exceptionally low number of reported failures in the literature makes Implanon/Nexplanon the most effective hormonal contraceptive available.
Because pregnancy is so rare with this method, ectopic pregnancy is also extremely uncommon.

Compared with studies of implants, fewer injectable studies report pregnancy location. This may be because very low incidence of ectopic pregnancy among users of these methods makes it unnecessary to clarify that all reported pregnancies are intrauterine. While we cannot be certain that this is the case, the fact that only six reports of ectopic pregnancy in three studies exist in nearly 50 years of published literature on progestin injectables supports such an assumption. Furthermore, each of the three injectable studies that report ectopic pregnancy have important limitations, including incomplete data [82], use of very low dose of progestin [93] and a confounding risk factor for ectopic pregnancy [85].

The clinical and epidemiological evidence indicate that LNG-containing implants are more likely to result in an ectopic pregnancy (or any pregnancy) than the ENG implant or progestin-only injectables. The type and dose of progestin resulting in various levels of ovarian suppression may play a role. Implanon/Nexplanon, DMPA and NET-EN more completely suppress ovulation, thus limiting the potential for fertilization and implantation to occur in any location. Studies of Implanon indicate that only 4% of Implanon users ovulate by the end of the method’s 3-year recommended duration of use [109]. In contrast, among LNG implant users, ovulation is suppressed only initially but then resumes in many. By year 5 of use, more than half of Norplant users ovulate regularly [110], and it is estimated that Jadelle use suppresses ovulation in only 45–85% of menstrual cycles [111]. Case studies (not included in this review) reporting ectopic pregnancies in Implanon users who may have lower plasma concentration of ENG due to drug interaction with certain antiretrovirals or other drugs known to induce hepatic enzymes [112–115] and, therefore, do not fully suppress ovulation support this theory, as does the higher rate of ectopic pregnancies among users of a lower-dose LNG implants [62].

While ovulation is more fully suppressed with use of progestin injectables [116], contraceptive failure rates are higher with DMPA and NET-EN than with implants. This could be explained by the fact that, unlike implants, these methods depend on women’s ability to use them correctly, that is, come back for reinjection on time. Nevertheless, in spite of the higher failure rate, very few reported pregnancies among injectable users are ectopic. Why method failure with use of injectables is less likely to lead to ectopic pregnancy than LNG implants is unknown but could be related to the particular effects the different progestins have on target tissues, including the fallopian tubes.

Research primarily from the field of assisted reproduction shows that sex steroids play a crucial role in regulating the number and activity of ciliated cells in the fallopian tubes, the primary mechanism of gamete and zygote transport [117]. Fallopian tubes containing an ectopic pregnancy show a marked reduction in the number of ciliated cells compared with those from women with an intrauterine pregnancy of the same gestational age [118]. In vitro studies of ciliary function have found that incubation with progesterone substantially reduces both ciliogenesis [12] and ciliary beat frequency [119] in fallopian tube cells in a dose-dependent fashion. It is likely that synthetic progestins affect ciliary development and activity in a similar way, although the effect of various progestins may differ due to their dose or structure/activity differences [120]. Current and future contraceptive development efforts may consider further exploration of the physiological mechanisms underlying ectopic pregnancy risk with specific progestins.

The goal of the present analysis was to review all published studies of implant and injectable progestin-only contraceptives in order to describe ectopic pregnancy risk with use of these methods. To obtain the most comprehensive information, we did not restrict by whether or not the method was ever marketed or by study design. Formal meta-analysis was not appropriate due to the heterogeneous study designs, outcome measures and study populations in the reviewed studies. One limitation of our review is that a number of studies, especially of injectables, did not report pregnancy location, and we cannot be sure that all reported pregnancies were intrauterine. In addition, due to the breadth of the review, we were unable to thoroughly assess the data quality and risk of bias for each of the 81 studies included in the review. Certainly, the ectopic pregnancy incidence rates reported in or calculated from the studies in this review could be influenced by many factors including length of study follow-up, ascertainment of outcomes in individual studies and underlying and unmeasured confounding risk factors in the studied populations.

Women who choose to use implant or injectable contraception can be assured that use of these methods substantially reduces their risk of pregnancy and, thus, ectopic pregnancy. The substantial body of research reviewed here shows that ectopic pregnancy risk among users of marketed implants and injectables is considerably lower than that of women who are not using contraception. While women who choose to use LNG-containing implants, such as Jadelle or Sino-implant (II), and their providers should be aware of potential signs of ectopic pregnancy in the small chance that the method should fail, fear of ectopic pregnancy should not be a deterrent for use or provision of these methods.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.contraception.2015.08.016.

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References


Merck & Co., Inc. Nexplanon: highlights of prescribing information.


Du M, Zheng H, Guo W. Five-year clinical observation of China-
Tseng LH, Lee TY, Yang YS, Ko TM, Chuang SM. Norplant
Lubis F, Prihartono J, Agoestina T, Sutedi H. One-year
Vekemans M, Delvigne A, Paesmans M. Continuation rates with a
Chaudhury N, Gupta AN, Hazra MN, Hingorani V, Kochhar M, Buckshee K, Chatterjee P, Dhall GI, Kodkany MN, Lalitha K, Coutinho EM, Da Silva AR, Kraft HG. Fertility control with sub-
Coutinho EM, Ferreira DA, Prates H, Kinel F. Excretion of [6-
Coutinho EM, da Silva AR, Kraft HG. Fertility control with sub-
Coutinho EM, Da Silva AR, Kraft HG. Fertility control with sub-
Coutinho EM, da Silva AR, Mattos CE, Nielsen NC, Osler M, Wiese J. Contraception with long acting subdermal implants: II. Measured and


