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**ASK THE QUESTION**

**Question 1:** Does exposure to Depo Provera through utilization of “quick start” or same-day Depo Provera initiation or re-instate increase teratogenic risk to an undetected early pregnancy?

**Objective:** Review of documented teratogenic risks of Depo Provera exposure to an undetected fetus

**Background:** Patients requesting initiation of the injectable contraceptive Depo Provera will have, at times, recently had unprotected intercourse, thus introducing the chance that there could be an undetected pregnancy at the time of the request. This has required patients to return for the injection following a two week period of protected intercourse only. Unfortunately, this can increase the risk that the patient will become pregnant during the delay or not return for the injection at all, thus increasing the risk for an unplanned or undesired pregnancy.

**SEARCH FOR EVIDENCE**

**Search strategies** included articles published in English, publications within past 25 years, and research-based studies.

**Databases** included PubMed, Cochrane, CINHAL, and Google Scholar

**Key words/terms** Depo Provera, Medroxyprogesterone, injectable contraceptive, steroid contraceptive, teratogen, teratogenicity, exposure in pregnancy, fetal risk, immediate start, quick start, fetal development

**CRITICALLY ANALYZE THE EVIDENCE**
Question 1: Is in-utero exposure to Depo Provera harmful to the undetected fetus?

Grade Criteria: Same-Day or “Quick Start” initiation of Depo Provera should be cautiously utilized in presence of possible undetected pregnancy. Weak Recommendation, Low Quality Evidence.

Five studies were found evaluating the risks of exposure in utero to Medroxyprogesterone. Three studies focused on Depo Provera while two focused on Medoroxyprogesterone acetate. Results reveal significant risk to fetus including low birth weight (LBW) and neonatal and infant death when exposed to Depo Provera.

As the concern was for Depo Provera exposure, the two studies that focused on Medroxyprogesterone acetate were not included in the analysis.

One cohort study of 1573 pregnancies in Thailand with Depo Provera exposure found the risk for LBW were increased (OR: 1.5; 95%CI: 1.2-1.9). The risk increased when Depo Provera is administered within 4 weeks of conception (OR: 1.9; 95%CI: 1.4-3.2) (Pardthaison & Gray, 1991).

A second cohort study of 1431 women in Thailand with children exposed to Depo Provera in utero found a significantly increased risk of neonatal death (OR: 1.8; 95%CI: 1.1-3.0)) and infant death (OR: 2.0; 95% CI: 1.3-3.2). Adjustment for LBW decreased the risk (OR: 1.2; 95% CI: 0.8-1.9 and OR: 1.2; 95% CI: .08-1.8) respectively, suggesting LBW may act as an intermediate determinant in outcomes (Gray & Pardthaison, 1991).

A final cohort study of 1207 Thai children exposed to Depo Provera identifies an increased risk of suboptimal height, however socioeconomic factor adjustments reveal no risk among Depo Provera exposed children (RR: 1.4; 95% CI 1.2-1.8) (Pardthaison et al., 1992).

<table>
<thead>
<tr>
<th>PICO Question #1</th>
<th>Purpose of Study</th>
<th>Study Design</th>
<th>Sample Size/Patient Population</th>
<th>Outcomes</th>
<th>Design Limitations</th>
<th>Lower Quality Rating if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yovich et al., 1988</td>
<td>Evaluate potential teratogenicity of progestagens administered in first trimester</td>
<td>Matched series study</td>
<td>1016 pregnancies in 913 women from a sub fertile population; 449 were treated with medroxyprogesterone acetate</td>
<td>15/336 (4.1%) of infants in MPA treated group had congenital abnormalities, compared to 15/428 (3.5%) infants in untreated group (p &gt; 0.05)</td>
<td>Study Limitations = None</td>
<td>Studies inconsistent (When there are differences in the direction of effect, the size of the differences of effect, and the significance of the differences that cannot be reasonably explained)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Results</th>
<th>Study Limitations</th>
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<tbody>
<tr>
<td>Pardthaison &amp; Gray, 1991</td>
<td>Cohort study</td>
<td>1573 pregnancies with depo exposure; 830 accidental pregnancies and 743 after conception; and 2578 planned pregnancies with no steroid exposures</td>
<td>Adjusted OR for LBW were increased for accidental pregnancies with fetal exposure to depo-provera (OR: 1.5; 95% CI: 1.2-1.9); Risk of LBW was increased when conception was estimated to have occurred within 4 weeks of injection (OR: 1.9; 95% CI: 1.4-3.2)</td>
<td>None; Insufficient sample size; Lack of allocation concealment; Selective reporting of measures; Large losses to F/U</td>
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<tr>
<td>Katz et al., 1985</td>
<td>Controlled historic prospective study</td>
<td>2754 infants born to mothers who bled during first trimester of pregnancy; 1608 infants born to mothers treated with progestogens (mostly MPA), and 1146 infants of untreated mothers</td>
<td>Overall rate of malformations was 120 per 1000 in MPA group, and 123.9 per 1000 in control group (p=0.05); Major malformations occurred at rates of 63.4 and 71.5 per 1000 in MPA and control groups, respectively (p=0.05)</td>
<td>None; Insufficient sample size; Lack of allocation concealment; Selective reporting of measures; Large losses to F/U</td>
</tr>
<tr>
<td>Gray &amp; Pardthaisong., 1991</td>
<td>Cohort</td>
<td>1431 women in Thailand who used depo-provera, and 2307 control patients with no hormonal exposure</td>
<td>Odds ratio for neonatal death was significantly increased with depo-provera exposure due to accidental pregnancy (OR: 1.8; 95% CI: 1.1-3.0), and for infant death (OR: 2.0; 95% CI: 1.3-3.2); Adjustment for LBW reduced the risk, suggesting LBW may act as intermediate determinant of depo-provera associated mortality (Neonatal death: OR: 1.2; 95% CI: 0.8-1.9 and infant death OR:1.2; 95% CI: 0.8-1.8)</td>
<td>None; Insufficient sample size; Lack of allocation concealment; Selective reporting of measures; Large losses to F/U</td>
</tr>
</tbody>
</table>

Study Limitations = None; Insufficient sample size; Lack of allocation concealment; Selective reporting of measures; Large losses to F/U

Studies are indirect: (Your PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)

Studies are imprecise: (When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)

Publication Bias: (e.g. pharmaceutical company sponsors study on effectiveness of drug)

Increase Quality Rating if: Large Effect

Level of evidence for studies as a whole: High, Moderate, Low, Very Low
To investigate the effects of in utero exposure to depo-provera and oral contraceptives on long-term growth and development outcomes for children

Cohort

1207 Thai children exposed to depo-provera; and 1167 patients in control group

Children with exposure to depo-provera during pregnancy and lactation had an increased risk of suboptimal growth in height (RR: 1.4; 95% CI: 1.2-1.8)

However, after adjusting for socioeconomic factors, there was no increased risk for impaired growth among depo-provera exposed children (RR:1.1; 95% CI: 0.8-1.6)

Study Limitations = None
Insufficient sample size
Lack of blinding
Stopped early for benefit
Lack of allocation concealment
Selective reporting of measures
Large losses to FU

APPLY THE EVIDENCE

- The results of the studies of risk to fetus following exposure to Depo-Provera in utero indicate a significant risk for LBW.
- Neonatal and infant death is noted to be a significant risk as well, however LBW seems to be the determinant and when this factor is removed risk drops significantly.
- Careful consideration should be made regarding risk of undetected pregnancy and exposure to Depo-Provera due to risk for LBW which significantly increases risk of mortality.

REFERENCES


