

Review Article

Evidence shift on Pregnancy risk of Progestins

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Abstract

Science is ever changing. Evidences developed and practiced are becoming far less than evidences, when new generation of evidences comes. There are many reasons for evidence shifts. Here we are discussing a classic example of use of progesterone in pregnancy; where inappropriateness of study methodology was the reason for producing wrong evidence for a long period of time. In 1970's many studies came out with birth defects due to use of progesterone in pregnancy, which resulted in a warning recommended by FDA; but those studies were largely inconclusive or methodologically wrong. Further scientific studies resulted in a remarkable evidence shift; that there was no detectable risk of congenital abnormalities in the offspring of mothers with progesterone treatment during early pregnancy. Progesterone reduces the rate of spontaneous early preterm delivery and prevents recurrent miscarriage. Progesterone is also commonly used after embryo transfer during in vitro fertilization in present time. Evidence shifts have no end until medicine remains incomplete.

Key words: Evidence shift, Progesterone, Pregnancy risk

Introduction

Progesterone was found to be one of the basic hormones of adaptation and of resistance to stress. In a case of

progesterone deficiency, too much cortisol is produced, and excessive cortisol causes

osteoporosis, aging of the skin, damage to brain cells, and the accumulation of fat, especially on the back and abdomen.¹ Progesterone serves as a precursor to the estrogens, androgens, and adrenocortical steroids.²

While considering hormone balancing, when estrogen becomes dominant and progesterone is deficient, the estrogen can potentially become toxic to the body; thus progesterone has a balancing or mitigating effect on estrogen. Progesterone is the body's natural anti-estrogen.³ Until approximately 7 weeks of gestation, increased progesterone production is dependent on the corpus luteum and thereafter on the placenta, the so-called "luteal-placental shift" which occurs between 7 and 10 weeks.⁴

The withdrawal of progesterone at the end of the non-fertile cycle leads to changes in the endometrial extracellular matrix and constriction of spiral arteries, resulting in menstruation.⁵ Progesterone is the body's natural anti-estrogen. Elevations in serum levels of progesterone is an indirect evidence of ovulation.⁶

Fraenkel showed in 1903 that destruction of the corpora lutea in pregnant rabbits caused abortion.⁷ The dominant role of

Calicut Medical Journal 2010; 8(1):e4

progesterone in pregnancy is due to the fact that progesterone protects the allogenic conceptus from immunological rejection by the mother.⁸ Alpha Hydroxy-Progesterone

Caproate (17P) treatment reduces cervical shortening inhibiting cervical Interleukin-1 secretion, is the first to address the relationship between progesterone, cervical changes, and preterm deliveries.⁹

In the late 1960s and 1970s, a number of epidemiological studies were published indicating that pregnant women who were exposed to an array of sex steroids delivered infants with an increased incidence of nongenital congenital malformations. Because of these publications, the U. S. Food and Drug Administration (FDA), in conjunction with various pharmaceutical companies, labeled the therapeutic exposure of progestational drugs and contraceptives in pregnant women as a risk factor for limb-reduction defects (LRDs) and congenital heart defects (CHDs).¹⁰

Natural and Synthetic Progestins

Progesterone is the only natural progestin [Compounds with biological activities similar to those of progesterone are referred to as progestins, progestational agents, progestagens, progestogens, gestagens or gestogens.⁷] with any significant biologic activity. Natural progesterone is available in two oral forms: crystalline progesterone (which is poorly absorbed when swallowed), and a micronized form, which is better absorbed orally. Vaginal and intramuscular preparations are also available.⁴

Progesterone is now synthetically made but it behaves just like the body's natural progesterone once it is absorbed into the

blood stream. This is to be distinguished from synthetic progesterone-like chemicals called progestogens which bind to the body's progesterone receptors and function for the most part, just like progesterone. As they are chemically different from natural progesterone, they sometimes have side effects or actions that are different than progesterone.¹¹

Synthetic progestins, which are more potent, are divided into either progesterone-like or testosterone-like compounds. Those structurally similar to progesterone include 17 alpha-hydroxyprogesterone acetate, medroxyprogesterone acetate (MPA), megestrol acetate, and cyproterone acetate. Those structurally similar to testosterone are then further divided into two classes: those related to norethindrone (norethindrone acetate, ethynodiol acetate, norethynodrel, and norethindrone enanthate); and those related to levonorgestrel (desogestrel, norgestimate, and gestodene, often referred to as "new generation" progestins).⁴

In contrast to some of the progestogens such as medroxyprogesterone acetate, natural progesterone does not seem to suppress good cholesterol (HDL), has no effect on blood pressure or mood, and shows less of a tendency to cause increased male-hormone-like effects such as facial hair growth. Each synthetic progestogen may have a somewhat different side-effect profile also and hence it is not easy to generalize.¹¹ Synthetic progestins are categorized as pregnancy risk category 'X' (contraindicated) where as natural progesterone is now categorized as pregnancy risk category 'B' (with no proven risk from studies). A few months back even natural progesterone was categorized as pregnancy risk category 'X'.^{12 & 13}

Early evidence of risk

Risk as contraceptive:

Ectopic pregnancies are more likely to occur in those who take oral progesterone-only contraceptives compared to who do not take hormonal contraceptives at all. Oral progestogen-only contraceptives do not reliably inhibit ovulation and therefore offer less protection against ectopic pregnancy than against intra-uterine pregnancy. Meta analysis (Bracken, 1990) of some studies, confirmed that relative risk of all malformations with use of oral contraceptives was estimated to be 0.99 (95% confidence intervals 0.83 to 1.19). The use of oral contraceptives in early pregnancy also appears unlikely to increase the risk of hypospadias in male fetuses.¹⁴

Risk as drug in pregnancy:

In 1977, the FDA recommended to restrict the use of progestogens in early pregnancy, based on early studies that showed that MPA might cause defects in cardiac development, CNS effects, amelia, and masculinization of female fetuses. Other investigators found a dose-related induction of cleft palate by excessive dosing of MPA in rabbits, but not in mice or rats. In one of the studies (Suzan L. Carmichael, 2005) it was found that pregnancy-related intake of progestins was associated with increased hypospadias risk. Cases of hepatocellular disease have been reported rarely in women treated with progesterone during the second and third trimester.¹⁴

Medications like progesterone may cause abnormal blood clotting. This may cut off the blood supply to the brain, heart, lungs, or eyes and cause serious problems.¹⁵ For example; a 30-year-old woman developed a retinal artery occlusion after taking high-

dose IM progestogen for 2 weeks to prevent a threatened miscarriage.⁴ These early studies were often contradictory and inconclusive, chiefly due to a lack of uniformity of study material and different methodologies.⁴

The Evidence Shift

Many subsequent and better-designed studies, however, have failed to show any such harmful effect. One of the larger studies evaluated 2,754 infants born to women who experienced vaginal bleeding during their first trimester. During the first 3 months of pregnancy, 1,608 women received progestin (mostly MPA) therapy, and the control group comprised 1,146 infants of untreated mothers. There was no difference in the malformation rate between the two groups (120/1,000 vs. 123.9/1,000). This study was followed by an evaluation of 1,016 pregnancies in which 449 women received MPA from the 5th to 7th week of pregnancy. Once again, no differences were found with regards to congenital abnormalities in the treated versus untreated group. Based on such data, progesterone doesn't seem to put an embryo at risk, nor is it likely to cause an abnormal fetus to be retained that might otherwise abort.⁴

The American College of Obstetricians and Gynecologists objected to the initial FDA labeling of progestogens, stating "there are no data to indicate that the use of progesterone causes any teratogenic effects and is disturbing to infertility patients taking progesterone."⁴

In 1987 the FDA held a hearing in which the FDA, the Teratology Society, the Centers for Disease Control and Prevention, the American College of Obstetrics and

Calicut Medical Journal 2010; 8(1):e4

Gynecology, and other organizations supported the position that progestational agents did not result in nongenital malformations. Hence in 1999 the FDA published the new wording for package inserts that removed warnings for nongenital malformations for all progestational agents.¹⁰

Researchers at the 27th Annual Society for Maternal-Fetal Medicine (SMFM) meeting announced that high-dose progesterone treatment helped at-risk pregnant women avoid premature delivery.⁸ A preterm birth can have serious consequences to the baby, including cerebral palsy, mental retardation, lung disease, blindness and hearing loss.¹⁵

Conclusion

The recent evidence shows that any real risk to pregnancies conceived after cessation of

oral contraception is very small and outweighed by the undoubted advantages of its use. We know that most of the congenital abnormalities are resulting from reasons other than drugs. In contemporary medicine, progesterone is vigorously marketed for the treatment of threatened abortion, prevention of recurrent miscarriage or in the support of the luteal phase in assisted reproduction programmes and in threatened preterm labour. Progesterone is found to be safer than synthetic progestogens. Rare adverse effects caused by either natural or synthetic progestational drugs are outweighed by their advantages when used in obstetric practice. Recent evidence shifts the FDA pregnancy risk category of progesterone. We are still unaware of any serious risk which may appear on a long-term basis.

References:

1. Peat Ray. Pregnancy News: Preterm Delivery Risk Reduced by High-dose Progesterone Treatment, www.RayPeat.com, 2007, 1. (Retrieved on: 03-05-09).
2. Chrousos George P.; Basic and Clinical Pharmacology, Katzung G. Bertram, McGraw-Hill, Singapore, 2007, 10th ed., 661.
3. Rollins Catherine P.; 'A woman's guide to using natural progesterone, Making plans pty Ltd., www.natural-progesterone-advisory-network.com, Revised edition, 2005, 11-12 (Retrieved on: 16-03-09).
4. Buster John E., and Laurie Jane McKenzie; Cover Story: Progesterone in early pregnancy: measuring it, giving it, Contemporary OB/GYN, 2004, 49, 60-75.
5. Kristof Chwalisz, Maria Claudia Perez, Deborah DeManno et al.; Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis, Endocrine Reviews, 2005, 26 (3), 423-438.
6. Mohan Battacharya Sudhindra; Mid-luteal phase plasma progesterone levels in spontaneous and clomiphene citrate induced conception cycles, J Obstet Gynecol India, 2005, 55 (4), 350-352.
7. Loose David S. and Stancel George M. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Laurence Brunton L., John Lazo S., Keith Parker C. et. al., McGRAW-HILL Medical publishing Division, New York, 2006, 11th ed., 1541, 1558-1559.
8. Schindler Adolf E.; Pregnancy failure after spontaneous conception or ovulation induction: endocrine causes and treatment, Middle East Fertility Society Journal, 2004, 9 (1), pp. 3-9.
9. High-dose progesterone treatment helps at-risk pregnant women avoid premature delivery Women's Health News <http://www.marchofdimes.com/>, published: Sunday, 11-Feb-2007, (Retrieved on: 03-05-09).
10. Brent Robert L.; Nongenital malformations following exposure to progestational drugs: The last chapter of an erroneous allegation Birth Defects Research Part A, Clinical and Molecular Teratology, 2005, 73 (11), 906 – 918.
11. Frederick Jelovsek R.; Progesterone- its uses and effects www.wdxcyber.com, (Retrieved on: 16-03-09)
12. Hendrix Susan L.; The Merk Manual, Mark Beers H., Robert Porter S., Thomas Jones V. et al. Merk & Co. Inc., New Delhi, 2006, 18th ed., 2176.

Calicut Medical Journal 2010; 8(1):e4

13. Rxlist drug index; Progesterone Information-warnning and precautions, www.rxlist.com, (Retrieved on: 01-05-09).
14. Bracken M. B., Bonnar J., Roman-Wilms L. et.al; Martindale the Complete Drug Reference, Sweetman Sean C. Pharmaceutical Press, Great Britain. 2002, 33rd ed., 1454, 1458.
15. American Society of Health-System Pharmacists, Inc. Drug Information: Progesterone Disclaimer, <http://www.nlm.nih.gov/medlineplus/ashpdiscclaimer.html>, July 2004, (Retrieved on: 01-05-09).

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