DOI: 10.14744/etd.2018.18176

Manuscript Type: Original Article

Title: Hormonal Contraceptives: What If Exposed During Pregnancy?

Running Title: Hormonal contraceptives in pregnancy

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Cite this article as: Altıntaş Aykan D, Ergün Y. Hormonal Contraceptives: What If Exposed During Pregnancy? Erciyed Med J 2019; DOİ: 10.14744/etd.2018.18176

ABSTRACT

Objective: Hormonal contraceptives are contraindicated in pregnancy. However, some women may become pregnant while using contraceptives to prevent pregnancy. In addition, these hormones may be used for abnormal uterine bleeding or secondary amenorrhea. In this study, we evaluated fetal outcomes of pregnant women who were inadvertently exposed to hormonal contraceptives during anytime in pregnancy. We aimed to expand data about contraceptives concerning their potential teratogenic effects.

Methods: We collected data of pregnant women who had admitted to Teratology Information Service between 2014 and 2018 with hormonal contraception exposure during pregnancy. Data about medications, exposure to other agents and co-morbidities were documented. We analyzed the exposed drugs in terms of their potential teratogenic effects. Follow-up was conducted with the women after delivery to obtain whether any major or minor congenital malformations or adverse neurodevelopmental effects occurred in the infants.

Results: A total number of 25 pregnant women admitted to Teratology Information Service for inadvertent use of hormonal contraception during pregnancy. After delivery, we found that one female baby, exposed to medroxyprogesterone acetate in utero, had exitus postnatally in the first week of life. Three infants with maternally exposure to medroxyprogesterone acetate, dydrogesterone, estradiol valerate+norgestrel, and ethinyl estradiol+gestoden were born preterm. Among them, two infants with maternally exposure to medroxyprogesterone acetate and ethinyl estradiol+gestoden had low birth weight. On the other hand, we found that 75% of infants delivered were female.

Conclusion: Contraceptive hormones presented no major teratogenic effects. However, avoidance of hormonal exposure and discontinuation whenever possible during pregnancy is suggested.

Keywords: Contraception; Teratogens; Abnormalities, Drug-Induced; Pregnancy

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INTRODUCTION

Hormonal contraceptives, also known as birth control pills, provide reliable contraception and several contraceptive unrelated benefits. The decrease in their estrogen and progestin contents had led to a decrease in cardiovascular side effects (1). Due to their ease of use, these preparations are reliable option for the vast majority of women in contraception. Their action is to suppress the secretion of gonadotropin-releasing hormone (GnRH) from hypothalamus and gonadotropins from pituitary gland. The outstanding mechanism is the prevention of ovulation through the inhibition of the midcycle luteinizing hormone (LH) surge. In addition, these agents inhibit ovarian folliculogenesis by suppressing follicle-stimulating hormone (FSH) secretion from the pituitary gland (2).

Hormonal contraceptives are frequently prescribed for abnormal menstrual bleedings, hyperandrogenism, hormone replacement therapy, primary ovarian failure and polycystic ovary syndrome on behalf of contraception. Women who learn about their pregnancies while on contraception therapy are concerned that the drug may have negative effects on the fetus due to hormonal components. In the literature, these agents are notified not for use in pregnant women. Most products are defined as contraindicated in women who are pregnant or suspected to be pregnant. Some patterns of genital anomalies such as hypospadias in male babies and clitoral enlargement and labial fusion have been reported in female babies who were exposed to hormones in utero during the first trimester (3). Based on this data, in case of pregnancy, treatment should be discontinued. On the other hand, these agents were not related to major fetal or maternal side effects when used inadvertently in early pregnancy (4).

In this study, we aimed to investigate the potential effects of hormonal contraceptives on neonatal outcomes of women who had been exposed to these agents without being aware of

their pregnancy. The neonatal outcomes include fetal abnormality, major and/or minor birth defects, postnatal complications and delivery circumstances.

METHODS

This study included 25 pregnant women, who had admitted to the Teratology Information Service (TIS) between 2014 and 2018 for teratogenic risk analysis of hormonal contraceptives exposed inadvertently during their pregnancies. The study was approved by the Ethics Committee of Clinical Trials of the Faculty of Medicine (Approval Date: 24.10.2018; Approval No: 2018/19/14).

Information about the hormonal contraceptives used by the pregnant women was recorded by using a structured registration form. In addition to the active substance of the hormonal contraceptives, all other agents used concomitantly (herbs and drugs exposed in the acute or chronic process), radiation exposures, smoking and alcohol consumptions were documented. Data about the contraceptive doses, administration routes, amounts, indications, start and expiry periods, women's ages, races and education levels were questioned. The gestational week was calculated based on ultrasonography (USG) or the last menstrual period. This information was taken face to face at first contact with the TIS. After the expected date of birth, women were contacted by telephone to collect neonatal outcomes. The type of delivery, gestational age at delivery, birth weight, neonatal sex, the presence of any congenital anomalies or neurobehavioral disorders were recorded.

Statistical analysis

The data was analyzed using the SPSS 17.0 program. Continuous variables were expressed as median (range).

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RESULTS

Data about pregnant women

Between 2014 and 2018, a number of 25 cases with inadvertent exposure to hormonal contraceptives in pregnancy were identified. The ages of pregnant women range between 23 and 35 years. All were Turkish citizens, living in Kahramanmaraş province, except two women were from Gaziantep. Their educations were primary or elementary level. The median gestational age at the first contact to TIS was eight weeks (range: 5 - 23). There was no exposure to radiation, cigarette, alcohol or herbal. Contraceptive agent subtypes used by the pregnant women in this study were: Medroxyprogesterone acetate 5 mg (n=9), estradiol valerate 2 mg + norgestrel 0.5 mg (n=4), ethinyl estradiol 0.03 mg + levonorgestrel 0.15 mg (n=4), ulipristal 30 mg (n=2), medroxyprogesterone acetate 150 mg/ml (n=2), ethinyl estradiol 0.02 mg + gestoden 0.075 mg (n=2), **norethisterone enanthate 50 mg** + estradiol valerate 5 mg (n=1), desogestrel 75 µg (n=1), progesterone 50 mg/ml (n=1), dydrogesterone 10 mg (n=1), norethindrone 5 mg (n=1), given that one woman had used one or more types of agents. The hormonal contraceptives had been used for the following indications: Abnormal uterine bleeding (n=13), contraception (n=9), emergency contraception (n=2), and secondary amenorrhea (n=1). Data about pregnant women were shown in Table 1.

Patterns of contraceptive exposure

All pregnancies were treated at standard doses. The administration routes were per oral and intramuscular. The median start time of exposures was 3.5 weeks, and median expiry week was five. The gestational age at the beginning of contraception exposure range between <0 and

eight weeks, and expiry week range between <0 and 11 weeks. We found that 22 women were exposed the contraceptives in the first trimester, and three women in the preconception period. Patterns of contraceptive exposure were presented in Table 2.

Data about delivery and neonatal outcomes

We reached 16 women after the expected date of delivery. Among them, all infants were born healthy, except one infant had died at the first postnatal week. She was a premature female baby, born at the 32nd gestational week. Among living 15 infants, nine had been delivered by cesarean, and the other six infants were by vaginal delivery. The median gestational age at birth was 38 weeks (range: 32 - 41). The median weight at birth was 3200 g (range: 2000 - 4000). Gender of the newborns was 75 % female. Among living babies, three of them were preterm (gestational age< 37th week), and two were small for gestational age (SGA, birth weight < 2500 g). Data about delivery and neonatal outcomes were presented in Table 3.

DISCUSSION

In this study, we evaluated the pregnant women who were inadvertently exposed to hormonal contraceptives for theprevention of pregnancy or other underlying obstetric disorders. A total number of 25 pregnant women had admitted to our TIS for inadvertent exposure to hormonal contraception during pregnancy. We analyzed their medications and evaluated the drugs for the risk of teratogenic effects. After delivery,among 16 women that we could reach, we found that one female baby had died postnatally in the first week of life, three infants were born preterm, and two infants were SGA. The most common contraceptives used by the pregnant women in this study were medroxyprogesterone acetate, pharmaceutic combination

form of estradiol valerate + norgestrel, and pharmaceutic combination form of ethinyl estradiol + levonorgestrel.

Medroxyprogesterone acetate suppresses the gonadotropin release and inhibits ovulation (5). It has oral and intramuscular depot forms. In our study, nine women had used medroxyprogesterone acetate 5 mg oral tablet, and two women were treated with medroxyprogesterone acetate 150 mg/ml intramuscular formula. Male and female pseudohermaphroditism, clitoral hypertrophy and epispadias in infants with maternal exposure to medroxyprogesterone acetate were reported in previous studies (6). It was reported that progesterone receptor mRNA expression, increased in male fetuses and decreased in female fetuses due to medroxyprogesterone acetate exposure in utero, interacts with the androgen receptor in the development of possible abnormal genital tubercle (6).

There was also a controlled human studywhich did not find an association between maternal exposure to medroxyprogesterone acetate treatment with an increase in congenital malformations (7). In an evaluation of depot medroxyprogesterone acetate exposed births, a rise in the number of infants with low birth weight (<2500 g) was identified compared to controls (8). On the other hand, progesterone is known to inhibit basal and TNF-alpha-induced apoptosis in fetal membranes to prevent preterm labor (9). In our study, we found that 11 women used medroxyprogesterone acetate in the first trimester. Among their outcomes, one infant was born preterm (at the36thweek of gestation) with low birth weight (2000 g), and one female baby born preterm at the 32nd week had died postnatally in the first week of life. These women were both concomitantly exposed to diclofenac during the first six weeks of their pregnancies. The use of nonsteroidal anti-inflammatory drugs close to conception, including diclofenac, is reported to be related with increased abortion risk (10).

Ethinyl estradiol is a synthetic estrogen that is widely used to treat menopausal symptoms and menstrual disorders, and can be used in combination with a progestin for contraception. The frequency of congenital anomalies was not significantly increased among the infants of women who used ethinyl estradiol in combination with a progestin during pregnancy (4). In our study, the women with exposure to estradiol components gave birth to six term healthy and two preterm infants (at the 35th week).

Levonorgestrel is a frequently used progestin for emergency contraception (11). It can prevent or delay ovulation, increases the thickness of the cervical mucus and disrupts the corpus luteum formation (12). Recent studies showed that preovulatory levonorgestrel administration can lead to post-fertilization luteal effects and may explain its clinical effects when used before ovulation (13). In a follow-up study, children exposed to levonorgestrel were compared to a control group of children over a period of two years. No differences were observed in physical growth, mental development, or birth defects between these two groups (14). In addition, an increase in nongenital anomalies was not found after norgestrel nor levonorgestrel exposure in pregnancy (15). In our study, a combination of ethinyl estradiol + levonorgestrel was used by four women in the first trimester and they gave birth to healthy infants.

Body weight should be taken into consideration in the clinical effectiveness, as body weight alters the effectiveness of emergency contraception with levonorgestrel. Studies showed a significant reduction in the effectiveness of levonorgestrel emergency contraception in women with high body weight (16,17).

We found that 75 % of infants delivered subsequently were female. Hormonal contraception used before and in the early pregnancy may have increased the rate of the female gender, consistent with the results of one previous study (18). However, in some studies, no

significant differences were reported between the sex ratios of the infants whose mothers had been exposed to hormonal contraceptives, as compared to those of controls. In addition, no correlation was found between the sex of the fetus and the total duration of oral contraceptive used (19).

It is important to note the limitations of our study. First of all, the congenital abnormality rate was calculated using live newborns and terminated pregnancies due to congenital malformations, and therefore, the data may not represent all birth defects, such as those associated with miscarriages and stillbirths. We could not perform genetic analysis for possible chromosomal abnormalities in living babies, nor autopsy for the possible congenital malformation patterns of the case in postnatal exitus. Thus, the real teratogenic effect rate might be higher than that our data imply. Second, neonatal outcome data were obtained from patient telephone questionnaires rather than directly access to the medical record and neonatal examine. Physical examination of the infants and the first two years follow-up should be critical, since mothers may not have detailed medical information about the health of their babies. Third, the sample size in our study was too small. The small scale of our study requires further large scaled studies.

CONCLUSION

In this study of our data, hormonal contraceptives taken during pregnancy did not cause an increase on the risk of congenital malformations. We will expand our patient population and extend the postnatal follow-up time for advanced monitoring of the health status of infants and their neurobehavioral development. Thus, we will be able to get more remarkable results and counsel the pregnant women accordingly.

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Conflict of Interest: None

Financial Disclosure: None

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Table 1. Data about pregnant women

Age	Nation	Indication	Education (level)	USG (week)	Contraceptive
	TR	Secondary amenorrhea	-	9	MPA Progesterone
23	TR	Abnormal uterine bleeding	Elementary		Estradiol valerate +norgestrel
34	TR	Abnormal uterine bleeding	Elementary	12	Dydrogesterone Estradiol valerate + norgestrel
	TR	Abnormal uterine bleeding	-	5	MPA
34	TR	Contraception	Primary	12	Ethinyl estradiol +levonorgestrel
	TR	Abnormal uterine bleeding	-	6	MPA
	TR	Abnormal uterine bleeding	-	12	MPA
	TR	Abnormal uterine bleeding	-	6	MPA
35	TR	Abnormal uterine bleeding	Primary	5	Norethindrone
	TR	Abnormal uterine bleeding	-	12	MPA
	TR	Abnormal uterine bleeding	-	6	Estradiol valerate + norgestrel

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	TR	Emergency contraception	-	7	Ulipristal
	TR	Abnormal uterine bleeding	-	8	MPA
31	TR	Contraception	None	8	MPA
	TR	Abnormal uterine bleeding	-	8	MPA
25	TR	Contraception	Primary	10	Ethinyl estradiol + levonorgestrel Ethinyl estradiol + gestoden
26	TR	Contraception	Primary	**8**	**Norethisterone enanthate**+ Estradiol valerate
	TR	Contraception	-	7	Desogestrel
29	TR	Contraception	Primary	23	Ethinyl estradiol + gestoden
31	TR	Contraception	-	6	Ethinyl estradiol + levonorgestrel
34	TR	Abnormal uterine bleeding	Primary	7	Estradiol valerate + norgestrel
23	TR	Contraception	Elementary	7	Ethinyl estradiol+ levonorgestrel
26	TR	Emergency contraception	-	6	Ulipristal
28	TR	Contraception	Primary	8	MPA
	TR	Abnormal uterine bleeding	Elementary	7	MPA

USG: Ultrasonography, TR: Turkish, MPA: Medroxyprogesterone acetate

Table 2. Patterns of contraceptive exposure

Exposed contraceptive	**Dose**	**Route**	**Start week**	**Expiry week**	**Exposed period**
Medroxyprogesterone acetate 5 mg	2x1	p.o	4	5	1. trim
Progesterone 50 mg/ml	1x1	i.m	5	6	1. trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x 1	p.o	6	9	1. trim
Dydrogesterone 10 mg	2x1	p.o	4	6	1. trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	3	4	1. trim
Medroxyprogesterone acetate 5 mg	3x1	p.o	5	6	1. trim
Ethinyl estradiol 0.03 mg+levonorgestrel 0.15 mg	1x1	p.o	8	11	1. trim

Medroxyprogesterone acetate 5 mg	1x1	p.o	0	1	Before conception
Medroxyprogesterone acetate 5 mg	1x1	p.o	4	6	1. trim
Medroxyprogesterone acetate 5 mg	2x1	p.o	0	1	Before conception
Norethindrone 5 mg	3x1	p.o	2	3	1. trim
Medroxyprogesterone acetate 5 mg	2x1	p.o	4	5	1. trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	0	5	1. trim
Ulipristal 30 mg	1x1	p.o	5	6	1.trim
Medroxyprogesterone acetate 5 mg	1x1	p.o	4	5	1. trim
Medroxyprogesterone acetate 150 mg/ml	1x1	i.m	<0	<0	Before conception
Medroxyprogesterone acetate 5 mg	2x1	p.o	5	7	1. trim
Ethinyl estradiol 0.03 mg+ levonorgestrel 0.15 mg	1x1	p.o	0	5	1. trim
Ethinyl estradiol 0.02 mg+gestoden 0.075 mg	1x1	p.o	5	6	1. trim
Norethisterone enanthate 50 mg+estradiol valerate 5 mg	1x1	i.m	2	3	1. trim
Desogestrel 75 µg	1x4	p.o	3	4	1. trim
Ethinyl estradiol 0.02 mg+gestoden 0.075 mg	1x1	p.o	0	3	1. trim
Ethinyl estradiol 0.03 mg+levonorgestrel 0.15 mg	1x1	p.o	0	5	1. trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	0	5	1. trim
Ethinyl estradiol 0.03 mg+levonorgestrel 0.15 mg	1x1	p.o	0	6	1. trim
Ulipristal 30 mg	1x1	p.o	2	3	1.trim
Medroxyprogesterone acetate 150 mg/ml	1x1	i.m	7	8	1. trim

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Medroxyprogesterone acetate 5 mg	2x1	p.o	4	6	1. trim

p.o: per oral; i.m: intramuscular; trim: trimester

Table 3. Data about delivery and neonatal outcome

Exposed contraceptive	**Results**	**Delivery route**	**Gestational age (week)**	**Weight (gram)**	**Sex**
MPA Progesterone	Healthy	Cesarean	38	3600	
Estradiol valerate + norgestrel	Healthy	Cesarean	38	3850	Female
Dydrogesterone Estradiol valerate + norgestrel	Healthy	Cesarean	35	2700	Male
Ethinyl estradiol + levonorgestrel	Healthy	Cesarean	38	3000	Female
MPA	Healthy	Cesarean	40	3200	
Norethindrone	Healthy	Vaginal	41	3300	Female
MPA	Healthy	Cesarean	36	2000	Female
Ethinyl estradiol + levonorgestrel Ethinyl estradiol + gestoden	Healthy	Vaginal	39	3500	Female

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Norethisterone enanthate+ Estradiol valerate	Healthy	Vaginal	40	2800	Female
Desogestrel	Healthy	Vaginal	40	3300	Female
Ethinyl estradiol + gestoden	Healthy	Vaginal	35	2300	Male
Ethinyl estradiol + levonorgestrel	Healthy	Cesarean	39	4000	
Ethinyl estradiol+ levonorgestrel	Healthy	Cesarean	37	2800	Male
Ulipristal	Healthy	Cesarean	38	3400	
MPA	Postnatal exitus	Cesarean	32	-	Female
MPA	Healthy	Vaginal	40	3200	Female

MPA: Medroxyprogesterone acetate

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