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Hormonal Contraceptives: What if Exposed During Pregnancy?

ORIGINAL ARTICLE

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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 the present study, we evaluated the fetal outcomes of pregnant women who were inadvertently exposed to hormonal contraceptives during anytime in pregnancy. The aim of the present study was to expand the data about contraceptives with regard to their potential teratogenic effects.

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

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

Conclusion: Contraceptive hormones presented no major teratogenic effects. However, avoidance of hormonal exposure and discontinuation whenever possible during pregnancy are 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). Owing to their ease of use, these preparations are a reliable option for the vast majority of women using contraception. Their action is to suppress the secretion of gonadotropin-releasing hormone from the hypothalamus and gonadotropins from the pituitary gland. The outstanding mechanism is the prevention of ovulation through the inhibition of the midcycle luteinizing hormone surge. In addition, these agents inhibit ovarian folliculogenesis by suppressing follicle-stimulating hormone 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 its 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 in female babies who were exposed to hormones in utero during the first trimester, have been reported (3). Based on this data, treatment should be discontinued in case of pregnancy. On the other hand, these agents are not related to major fetal or maternal side effects when used inadvertently in early pregnancy (4).

The aim of the present study was to investigate the potential effects of hormonal contraceptives on the neonatal outcomes of women who had been exposed to these agents without being aware of their pregnancy. Neonatal outcomes include fetal abnormality, major and/or minor birth defects, postnatal complications, and delivery circumstances.

Table 1. Data about pregnant women

Age	Nationality	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
	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 +gestodene
26	TR	Contraception	Primary	8	Norethisterone enanthate+ estradiol valerate
	TR	Contraception	–	7	Desogestrel
29	TR	Contraception	Primary	23	Ethinyl estradiol +gestodene
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

MATERIALS and METHODS

Twenty-five pregnant women who were admitted to the Teratology Information Service (TIS) between 2014 and 2018 for teratogenic risk analysis of hormonal contraceptives exposed inadvertently during their pregnancies were included in the study. The study was approved by the Ethics Committee of Clinical Trials of the Faculty of Medicine (approval date: 10/24/2018, approval no.: 2018/19/14).

Information about the hormonal contraceptives used by pregnant women was recorded by using a structured registration form. In addition to the active substance of hormonal contraceptives, all other agents used concomitantly (herbs and drugs exposed in the acute or chronic process), radiation exposures, and smoking and alcohol consumptions were documented. Data about contraceptive doses, administration routes, amounts, indications, start and expiry periods, women's ages, races, and education levels were collected. The gestational week was calculated based on ultrasonography or the

Table 2. Patterns of contraceptive exposure

Exposed to contraceptive	Dose	Route	Start week	Expiry week	Exposed period
Medroxyprogesterone acetate 5 mg	2x1	p.o	4	5	1st trim
Progesterone 50 mg/ml	1x1	i.m	5	6	1st trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	6	9	1st trim
Dydrogesterone 10 mg	2x1	p.o	4	6	1st trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	3	4	1st trim
Medroxyprogesterone acetate 5 mg	3x1	p.o	5	6	1st trim
Ethinyl estradiol 0.03 mg+levonorgestrel 0.15 mg	1x1	p.o	8	11	1st trim
Medroxyprogesterone acetate 5 mg	1x1	p.o	0	1	Before conception
Medroxyprogesterone acetate 5 mg	1x1	p.o	4	6	1st trim
Medroxyprogesterone acetate 5 mg	2x1	p.o	0	1	Before conception
Norethindrone 5 mg	3x1	p.o	2	3	1st trim
Medroxyprogesterone acetate 5 mg	2x1	p.o	4	5	1st trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	0	5	1st trim
Ulipristal 30 mg	1x1	p.o	5	6	1st trim
Medroxyprogesterone acetate 5 mg	1x1	p.o	4	5	1st trim
Medroxyprogesterone acetate 150 mg/ml	1x1	i.m	<0	<0	Before conception
Medroxyprogesterone acetate 5 mg	2x1	p.o	5	7	1st trim
Ethinyl estradiol 0.03 mg+ levonorgestrel 0.15 mg	1x1	p.o	0	5	1st trim
Ethinyl estradiol 0.02 mg+gestodene 0.075 mg	1x1	p.o	5	6	1st trim
Norethisterone enanthate 50 mg+estradiol valerate 5 mg	1x1	i.m	2	3	1st trim
Desogestrel 75 µg	1x4	p.o	3	4	1st trim
Ethinyl estradiol 0.02 mg+gestodene 0.075 mg	1x1	p.o	0	3	1st trim
Ethinyl estradiol 0.03 mg+levonorgestrel 0.15 mg	1x1	p.o	0	5	1st trim
Estradiol valerate 2 mg+norgestrel 0.5 mg	1x1	p.o	0	5	1st trim
Ethinyl estradiol 0.03 mg+levonorgestrel 0.15 mg	1x1	p.o	0	6	1st trim
Ulipristal 30 mg	1x1	p.o	2	3	1st trim
Medroxyprogesterone acetate 150 mg/ml	1x1	i.m	7	8	1st trim
Medroxyprogesterone acetate 5 mg	2x1	p.o	4	6	1st trim

p.o: Per oral; i.m: Intramuscular; trim: Trimester

last menstrual period. This information was obtained face-to-face at first contact with the TIS. Women were contacted by telephone to collect neonatal outcomes after their expected date of birth. The type of delivery, gestational age at delivery, birth weight, neonatal sex, and the presence of any congenital anomalies or neurobehavioral disorders were recorded.

Statistical Analysis

Data were analyzed using the SPSS 17.0 program (SPSS Inc., Chicago, IL, USA). Data were expressed as median (range) for continuous variables.

RESULTS

Data About Pregnant Women

Twenty-five cases with inadvertent exposure to hormonal contraceptives in pregnancy between 2014 and 2018 were identified. The age of pregnant women was between 23 and 35 years. All were Turkish citizens living in Kahramanmaraş province, except for two women who were from Gaziantep. Their education levels were primary or elementary level. The median gestational age at the first contact with the TIS was 8 (5–23) weeks. There was no exposure to radiation, cigarette, alcohol, or herb. In the present study, the contraceptive agent subtypes used by pregnant women included 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+gestodene 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), and norethindrone 5 mg (n=1), provided that one woman had used one or more types of agents. 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). Table 1 shows the data about pregnant women.

Patterns of Contraceptive Exposure

All pregnancies were treated at standard doses. The administration routes were oral and intramuscular. The median start time of exposures was 3.5 weeks, and the median expiry week was 5 weeks. The gestational age at the beginning of contraception exposure

Table 3. Data about delivery and neonatal outcome

Exposed to contraceptive	Results	Delivery route	Gestational age (week)	Weight (gram)	Sex
MPA	Healthy	Cesarean	38	3600	
Progesterone					
Estradiol valerate+norgestrel	Healthy	Cesarean	38	3850	Female
Dydrogesterone	Healthy	Cesarean	35	2700	Male
Estradiol valerate+norgestrel					
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	Healthy	Vaginal	39	3500	Female
Ethinyl estradiol+gestodene					
Norethisterone enanthate+estradiol valerate	Healthy	Vaginal	40	2800	Female
Desogestrel	Healthy	Vaginal	40	3300	Female
Ethinyl estradiol+gestodene	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

ranged between <0 and 8 weeks, and expiry week ranged between <0 and 11 weeks. We found that 22 women were exposed to contraceptives in the first trimester, and 3 women in the preconception period. Table 2 presents the patterns of contraceptive exposure.

Data About Delivery and Neonatal Outcomes

We reached 16 women after the expected date of delivery. Among the infants of 16 women, all infants were born healthy, except for 1 infant who died at the first postnatal week. She was a premature female baby born at gestational week 32. Among the living 15 infants, 9 had been delivered by cesarean, and the other 6 infants were by vaginal delivery. The median gestational age at birth was 38 (32–41) weeks. The median weight at birth was 3200 (2000–4000) g. Gender of the newborns was 75% female. Among the living 15 babies, 3 were preterm (gestational age <37 weeks), and 2 were small for gestational age (SGA, birth weight <2500 g). Table 3 presents the data about delivery and neonatal outcomes.

DISCUSSION

In the present study, we evaluated pregnant women who were inadvertently exposed to hormonal contraceptives for the prevention of pregnancy or other underlying obstetric disorders. A total of 25 pregnant women who were admitted to our TIS for inadvertent exposure to hormonal contraception during pregnancy were included in the study. We analyzed their medications and evaluated the drugs for the risk of teratogenic effects. Among the 16 women that we could reach after delivery, we found that 1 female baby had died postnatally in the first week of life, 3 infants were born preterm, and 2 infants were SGA. In the present study, the most common contraceptives used by pregnant women were medroxyprogesterone acetate, pharmaceutical combination form of estradiol valerate+norgestrel, and pharmaceutical combination form of ethinyl estradiol+levonorgestrel.

Medroxyprogesterone acetate suppresses 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 a possible abnormal genital tubercle (6).

A controlled human study did not find an association between maternal exposure to medroxyprogesterone acetate treatment and an increase in congenital malformations (7). In an evaluation of depot medroxyprogesterone acetate-exposed births, an increase in the number of infants with low birth weight (<2500 g) was identified compared with controls (8). On the other hand, progesterone is known to inhibit basal and tumor necrosis factor-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 the outcomes of 11 women, 1 infant was born preterm (36 weeks of gestation) with low birth weight (2000 g), and 1 female baby born preterm (32 weeks) had died postnatally in the first week of life. These women were both concomitantly exposed to diclofenac during the first 6 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 progestin for contraception. The frequency of congenital anomalies was not significantly increased among the infants of women who used ethinyl estradiol in combination with progestin during pregnancy (4). In our study, women with exposure to estradiol components gave birth to six term healthy and two preterm infants (35 weeks).

Levonorgestrel is a frequently used progestin for emergency contraception (11). It can prevent or delay ovulation, increase the thickness of the cervical mucus, and disrupt 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 with a control group of children over a period of 2 years. There were no differences 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 considered in the clinical effectiveness, as body weight alters the effectiveness of emergency contraception with levonorgestrel. Previous studies showed a significant decrease in the effectiveness of levonorgestrel emergency contraception in women with high body weight (16, 17).

We found that 75% of the infants delivered subsequently were female. Hormonal contraception used before and in early pregnancy may have increased the rate of the female gender; this is consistent with the results of a 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 compared with those of controls. In addition, no correlation was found between the sex of the fetus and the total duration of oral contraceptive used (19).

Our study has limitations. First, 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 the possible chromosomal abnormalities in living babies or autopsy for the possible congenital malformation patterns of the case in postnatal exitus. Thus, the real teratogenic effect rate might be higher than our data imply. Second, neonatal outcomes were obtained from patient telephone questionnaires rather than direct access to the medical record and neonatal examination. Physical examination of the infants and the first 2 years of follow-up should be critical, since mothers may not have detailed medical information about the health of their babies. Finally, the sample size in our study was too small. Further large scale studies should be conducted in the future.

CONCLUSION

In conclusion, hormonal contraceptives taken during pregnancy did not cause an increased risk of congenital malformations. In the future, 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 obtain more remarkable results and counsel pregnant women accordingly.

Ethics Committee Approval: 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).

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