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RESEARCH ARTICLE

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PHARMACOVIGILANCE STUDY OF SIDE EFFECTS ASSOCIATED WITH LEVONORGESTROL -ETHINYL ESTRADIOL AND DEPOTMEDROXY PROGESTERONE ACETATE

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ABSTRACT

Background: Levonorgestrol & Ethinyl estradiol (COCs) and Depotmedroxy progesterone acetate (Depo-Provera) are commonly prescribed contraceptives by family planning centers in Pakistan and compliance to these agents is reducing day by day due to associated side effects.

Objective: Monitoring side effects associated with the use of hormone replacement therapy in contraception.

***Method*:** It was a population based retrospective study of 1149 cases, maintained on these contraceptives for minor side effects (nausea, vomiting, hair loss and weight gain) and were divided into, groups receiving Drug-I i.e. COCs (n=365; 45.9%) and Drug-II Depo-Provera (n=431;

54.1%). The occurrence of side effects were correlated with Age I (19-35 years) and Age II (36-50 years), and Duration I (6months-1 year) and Duration-II (1-2 years).

Results: Women receiving Drug-I (n=365) were more likely to show nausea than Drug-II, [OR= 1.26; 95% CI, 1.17-1.37]. The odd of vomiting of Drug-I was 1.83 times greater than Drug-II [95% CI, 1.62-2.10], vomiting was found more related with Age I, [OR=1.46; 95% CI, 1.100-1.942] and the risk of vomiting was high in Duration-I [OR= 3.32; 95% CI, 2.46-4.48]. Drug-I showed more hair loss than Drug-II, [OR=2.36; 95% CI, 2.27-3.49], and hair loss was found more associated with Age II [OR=1.932; 95% CI, 0.776-1.371], but its relation with duration and age was insignificant (p>0.05).The likelihood of weight gain was found more with Drug-II, Age I and Duration II at 95% CI with OR of 2.36, 2.88 and 1.431 ($p<0.05$) respectively.

Conclusion: The most commonly observed side effects with COCs were nausea, vomiting and hair loss, whereas weight gain was found more associated with Depo-Provera.

Keywords: Pharmacovigilance, side effects, Levonorgestrol -Ethinyl estradiol and Depotmedroxy progesterone acetate

1. INTRODUCTION:

According to WHO, side effects are defined as, any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological property of the drug and pharmacovigilance studies play vital role to keep watch on and to reduce fundamentally drug related unwanted effects [1, 2]. Given the increasing utilization of COCs (Levonorgestrel and Ethinyl estradiol) and Depo-Provera (Depotmedroxy progesterone acetate) and the concurrent rise in associated side effects, this study was undertaken to assess the relationship between nausea, vomiting, hair loss, and weight gain and the usage of COCs and Depo-Provera. The aim is to enhance patient adherence and mitigate side effects. Confidence levels regarding the use of these contraceptives vary among women globally. Numerous researchers have conducted observational studies to address side effects, with the objective of averting issues linked to pharmacological interventions in diverse healthcare settings [3]. Present study evaluated the risk of minor side effects of COCs and Depo-Provera that can reduce the user confidence and cause drug discontinuation due to nausea, severe episodes of vomiting, hair loss and weight gain. It was estimated that 50% of pill discontinuations may occur due to side effects [4-9]. If used appropriately with good adherence i.e. 0.15 mg Levonorgestrol +0.03mg Ethinyl estradiol, the COCs failure rate for women of all ages, range between 6-8 pregnancies per 100 women in the first 12 months, have been reported [10, 11]. Nevertheless, prolonged use of COCs has been linked to an increased risk of cardiovascular diseases such as atherosclerosis, thromboembolism, and myocardial infarction. Additionally, reported complications include breast cancer, gallbladder disease, cervical cancer, and benign liver tumors, although these occurrences are uncommon [12]. Depot-medroxyprogesterone acetate 150mg is given every three months and has reported failure rate of 0.3 pregnancies per 100 women in the first 12 months of use [13]. Therefore the aim of this study was to determine the occurrence and relation of minor side effects caused by the regular use of Levonorgestrel & Ethinyl estradiol (COCs) and Depot-medroxy progesterone acetate (Depo-Provera) through multinomial logistic regression analysis. The age and duration of therapy related effects were also analyzed.

Logistic regression analysis serves as a potent method for examining research scenarios involving categorical outcome variables, particularly in medical research. It is particularly valuable when investigating dichotomous outcomes, such as the presence or absence of specific conditions, and correlating them with certain factors [14]. Many researchers have applied logistic regression model in medical research [15, 16]. Therefore in current study this statistical test was applied to correlate the likelihood of side effects with hormonal contraceptives, their duration of use and age of user.

The study aimed to observe the occurrence of adverse effects such as nausea, vomiting, hair loss, and weight gain among women using these contraceptives.

2. MATERIALS AND METHOD

The research was conducted across several family planning centers in Karachi, each staffed with a full-time gynecologist appointed by the Government of Pakistan. Prior to commencement, ethical approval was obtained from the Ethical Review Board at the University of Karachi. Female participants, who had been using hormonal contraceptives Drug-I and Drug-II for a minimum of two years, were recruited for the study.

1. Drug-I consisted of combined oral contraceptives (COCs) containing 0.15 mg Levonorgestrel + 0.03 mg Ethinyl estradiol, while
2. Drug-II was Depo-Provera (Depo), an injectable comprising 150mg/ml Medroxyprogesterone acetate.

A total of 1149 women, aged between 18 and 49, were included in the study and categorized into two age groups: Age I (19-35) and Age II (36-49). Additionally, they were grouped based on the duration of contraceptive use: Duration I (6 months-1 year) and Duration II (1-2 years).

2.1 Study population

Subjects were chosen based on inclusion and exclusion criteria established by various researchers, including Newhall WJ et al 1999 and Philbrick JT et al 1980. [17, 18].

Those selected individuals, who were using these agents, underwent a comprehensive assessment for minor side effects, and information was documented using a predefined data collection format. This format was designed following analogous studies conducted by other researchers [19]. Females meeting the inclusion criteria were assessed regarding their reproductive history.

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2.2 Inclusion criteria:

1. Women with age between 18 years to 50years receiving COCs and Depo for contraception.
2. Both new and women already maintained on COCs or Depo at the time of commencement of study.

2.3 Exclusion Criteria:

1. Women with a history of hypertension, elevated blood pressure, or other risk factors for adverse drug events before January 1, 2012, were identified using diagnostic information recorded in the database and were excluded from the source population.
2. Women aged below 18 and above 50 years were excluded.

The resulting study cohort comprised 1149 women who met the aforementioned inclusion criteria by using Drug-I and Drug-II. These enrolled individuals were assessed for the presence of minor side effects, such as nausea, vomiting, hair loss, and weight gain, associated with these contraceptive agents. The occurrence of side effects was monitored periodically, with evaluations conducted at every third-month follow-up visit. Among the 1149 cases, 365 women experienced one or more minor side effects attributed to Drug-I, while 431 cases were associated with Drug-II over the study period (from January 2012 to December 2013).

2.4 Statistical Analysis:

Multinomial logistic regression was applied using SPSS 20 and data was analyzed to determine odd ratios in order to assess the association between side effects and method of contraception as well as their occurrence with respect to age and duration of use. Beta regression coefficient values were calculated for each model against predictor variable (Drug), in order to observe the change in the occurrence of side effect with a unit change in predictor.

Ethical Approval:
The research have been ethically approved by the IERB committee of Jinnah University for Women, on 28th May 2014, with title of "Pharmacovigilance Study of Adverse Drug Reactions Associated with Hormonal Contraceptives".As the study was a part of PhD. Research; from which the research article have been extracted. The approval reference number is Ref No. JUW/IERB/PHARM-ARA-05/2014

Consent of Participants:
In our study "Pharmacovigilance Study of Side Effects Associated With Levonorgestrol -Ethinyl Estradiol and Depotmedroxy Progesterone Acetate," verbal consent was obtained from participants due to factors such as low literacy rates among a significant portion of the target population, hesitancy towards engaging with extensive written documentation among certain working women, and the need for standardized data collection procedures. This approach ensured inclusivity, allowing a broader representation of participants while maintaining consistency in consent procedures. Verbal consent discussions were conducted comprehensively to ensure participants' understanding of the study and their rights, aligning with ethical standards and maximizing data quality.

1. RESULTS

Association of Side effects with Drug-I and Drug-II:
When investigating the association between nausea and Drug-I (n=365) and Drug-II (n=431), it was found that 165 out of 364 cases (45.3%) and 199 out of 364 cases (54.7%) were attributed to each respective drug (Table 01). The chi-square value was calculated as 0.074 at a 95% confidence interval (CI) (p=0.01). The odds ratio (OR) obtained was 1.26 (1.17-1.37), indicating that the odds of experiencing nausea with Drug-I were 1.26 times higher than with Drug-II (Table 02). The omnibus test demonstrated a statistically significant association of nausea with Drug-I.

Table 1: Crosstab and Chi Square Test of Combined Oral Contraceptive (COCs) Verses Depo –Provera For Nausea

EFFECT OF DRUGS		**NAUSEA**		**TOTAL**
		Nausea Yes	Nausea No	
COCs[a](Drug-I)	Count	165	200	365
	% Nausea	45.3%	46.3%	45.9%
Depo-Provera[b](Drug-II)	Count	199	232	431
	% Nausea	54.7%	53.7%	54.1%
Total	Count	364	432	796
	% Nausea	100%	100%	100%
EFFECT OF AGE		**NAUSEA**		**TOTAL**
		Nausea Yes	Nausea No	
Age I (years) 19-35	Count	219	222	441
	%Nausea	60.2%	51.4%	55.4%
Age II (years) 36-50	Count	145	210	355
	%Nausea	39.8%	48.6%	44.6%
Total	Count	364	432	796
	%Nausea	100%	100%	100%
EFFECT OF DURATION		**NAUSEA**		**TOTAL**
		Nausea Yes	Nausea No	
Duration I (6months-1 year)	Count	264	183	447
	%Nausea	72.5%	42.4%	56.2%
Duration II (1-2 years)	Count	100	249	349
	%Nausea	27.5%	57.6%	43.8%
Total	Count	364	432	796

	%Nausea	100%	100%	100%

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b] Depro-Provera (Depotmedroxy progesterone acetate)

Table 2: Logistic Regression Predicting Nausea between Different Drugs, Age -Group and Duration

Description	**DRUGS Drug-I (COCs[a]) &Drug-II (Depo-Provera[b])**		**AGE Age I(19-35)&Age II (36-50)**		**DURATION Duration I (6months-1 year) & Duration II (1-2 years)**	
Number of reported cases	796		796		796	
Omnibus Tests of Model Coefficient s	Chi-Square	*p*-value	Chi-Square[c]	*p*-value	Chi-Square	*p*-value
	0.074	0.01	1.673	0.01	74.64	0.0001
Variables in the Equation	Drugs verses Nausea		Age verses Nausea		Duration verses Nausea	
	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower - Upper
	1.26	1.17 – 1.37	1.429	1.077-1.895	3.59	2.66-4.84
p-Value	0.01		0.013		0.0001	

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b] Depro-Provera (Depotmedroxy progesterone acetate)
[c] chi-square table value=3.84 (CI=95% and DF=1)

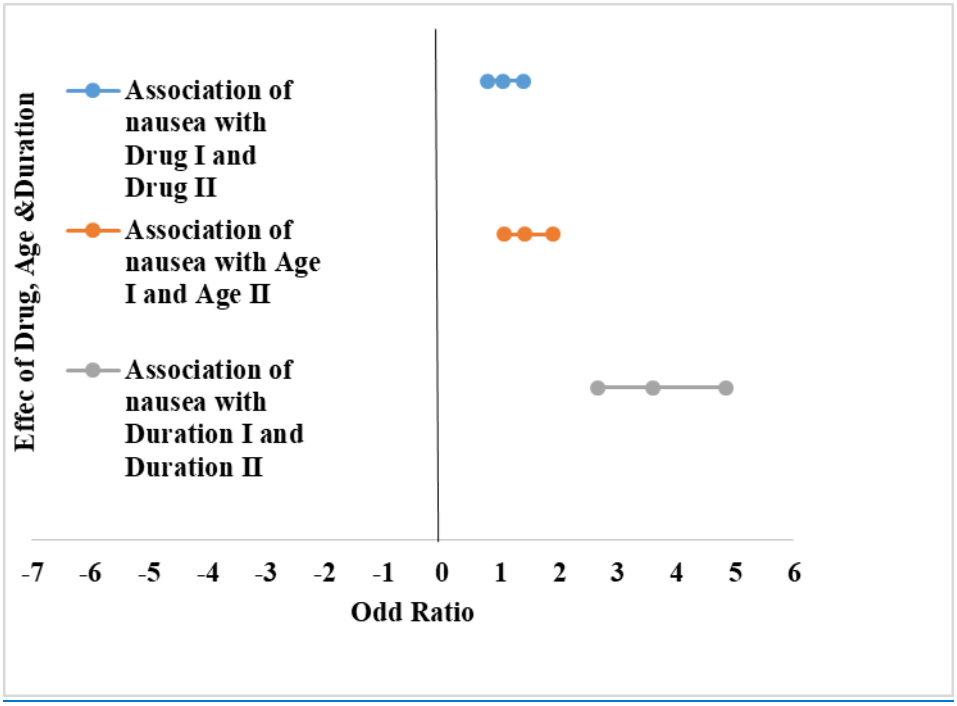

Figure 1: Association of Nausea with Drug, Age and Duration

Similarly, when examining the occurrence of vomiting, it was found that 45.3% of cases were associated with Drug-I and 56.7% with Drug-II (Table 03). The omnibus test yielded a chi-square value of 1.68 (p=0.01) at a 95% CI. The odds of vomiting with Drug-I were 1.8 times greater than with Drug-II (CI=95%, 1.62-2.10) (Table 04), indicating a significant association with Drug-I.

Table 3: Crosstab and Chi Square Test Of Combined Oral Contraceptive (COCs) Verses Depo –Provera For Vomiting

EFFECT OF DRUGS		**VOMITING**		**TOTAL**
		Vomiting Yes	Vomiting No	
COCs[a] (Drug-I)	Count	156	209	365
	% Vomiting	45.3%	47.9%	45.9%
Depo-Provera[b](Drug-II)	Count	204	227	431

	% Vomiting	56.7%	52.1%	54.1%
Total	Count	360	436	796
	% Vomiting	100%	100%	100%
EFFECT OF AGE		**VOMITING**		**TOTAL**
		Vomiting Yes	Vomiting No	
Age I (years) 19-35	Count	224	231	455
	% Vomiting	62.2%	53.0%	57.2%
Age II (years) 36-50	Count	136	205	341
	% Vomiting	37.8%	47.0%	42.8%
Total	Count	360	436	796
	% Vomiting	100%	100%	100%
EFFECT OF DURATION		**VOMITING**		**TOTAL**
		Vomiting Yes	Vomiting No	
Duration I (6months-1 year)	Count	263	196	459
	% Vomiting	73.1%	45.0%	57.7%
Duration II (1-2 years)	Count	97	240	337
	% Vomiting	26.9%	55.0%	42.3%
Total	Count	360	436	796
	% Vomiting	100%	100%	100%

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b] Depro-Provera (Depotmedroxy progesterone acetate)

Table 4: Logistic Regression Predicting Vomiting Between Different Drugs, Age Group and Duration

Description	**DRUGS Drug-I (COCs[a]) &Drug-II (Depo-Provera[b])**		**AGE Age I (19-35)& Age-II (36-50)**		**DURATION Duration I (6months-1 year) & Duration II (1-2 years)**	
Number of reported cases	796		796		796	
Omnibus Tests of Model Coefficient s	Chi-Square	*p*-value	Chi-Square[c]	*p*-value	Chi-Square	*p*-value
	1.68	0.019	6.89	0.009	65.19	0.0001
Variables in the Equation	Drugs verses Vomiting		Age verses Vomiting		Duration verses Vomiting	
	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower - Upper
	1.83	1.62 – 2.10	1.462	1.100-1.942	3.32	2.46-4.48
p-Value	0.01		0.009		0.0001	

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b]Depro-Provera (Depotmedroxy progesterone acetate)
[c] chi-square table value=3.84 (CI=95% and DF=1)

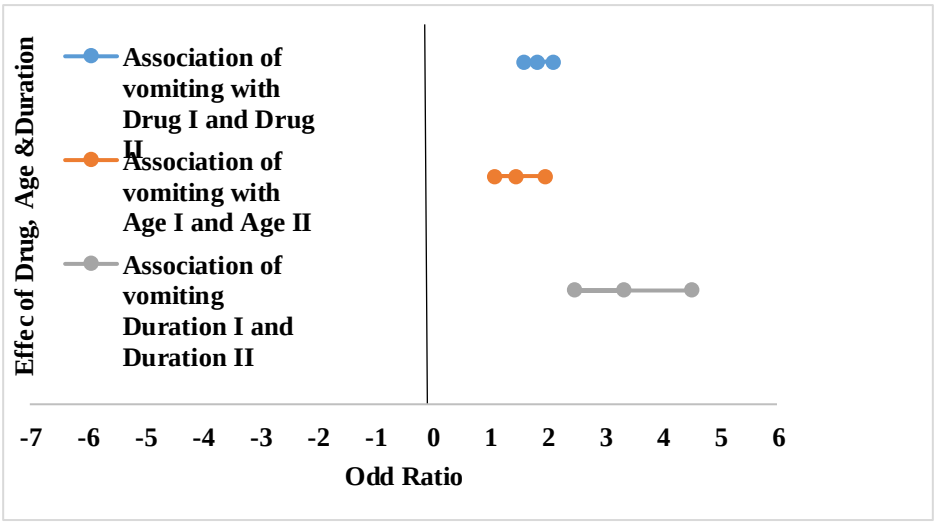

Figure 2: Association of Vomiting with Drug, Age and Duration

To assess the occurrence of hair loss among women using Drug-I and Drug-II, 47.0% and 53.0% of cases were identified, respectively (Table 05). The chi-square value was 43.43 (p=0.0001). The odds ratio (OR) obtained was 2.36, indicating that hair loss was more strongly associated with Drug-I than Drug-II (CI=95%, 2.27-3.49) (Table 06).

Table 5: Crosstab and Chi Square Test of Combined Oral Contraceptive (COCs) Verses Depo – Provera For Hair loss

EFFECT OF DRUGS		**HAIR LOSS**		**TOTAL**
		Hair loss Yes	Hair loss No	
COCs[a] Depo-Provera[b] (Drug-I)	Count	150	215	365
	% Hair loss	47.0%	45.1%	45.9%
Depo-Provera[b] (Drug-II)	Count	169	262	431
	% Hair loss	53.0%	54.9%	54.1%
Total	Count	319	477	796
	% Hair loss	100%	100%	100%
EFFECT OF AGE		**HAIR LOSS**		**TOTAL**
		Hair loss Yes	Hair loss No	
Age I (years) 19-35	Count	173	255	428
	% Hair loss	54.2%	53.5%	53.8%
Age II(years) 36-50	Count	146	222	368
	% Hair loss	45.8%	46.5%	46.2%
Total	Count	319	477	796
	% Hair loss	100%	100%	100%
EFFECT OF DURATION		**HAIR LOSS**		**TOTAL**
		Hair loss Yes	Hair loss No	
Duration I (6months-1 year)	Count	86	239	325
	% Hair loss	27.0%	50.1%	40.8%
Duration II (1-2 years)	Count	233	238	471
	% Hair loss	73.0%	49.9%	59.2%
Total	Count	319	477	796
	% Hair loss	100%	100%	100%

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b] Depro-Provera (Depotmedroxy progesterone acetate)

Table 6: Logistic Regression Predicting Hair Loss between Different Drugs, Age Group And Duration

Description	DRUGS Drug-I (COCs[a]) &Drug-II (Depo-Provera[b])		AGE Age I(19-35)& Age-II (36-50)		DURATION Duration I (6months-1 year) & Duration II (1-2 years))	
Number of reported cases	796		796		796	
Omnibus Tests of Model Coefficient s	Chi-Square	*p*-value	Chi-Square[c]	*p*-value	Chi-Square	*p*-value
	43.43	0.0001	0.046	0.830	4.62	0.830
Variables in the Equation	Drugs verses Hair loss		Age verses Hairloss		Duration verses Hair loss	
	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower - Upper
	2.36	2.27 – 3.49	1.532	0.776-1.371	1.033	0.776-1.371
p-Value	0.0001		0.830		0.830	

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b]Depro-Provera (Depotmedroxy progesterone acetate)
[c] chi-square table value=3.84 (CI=95% and DF=1)

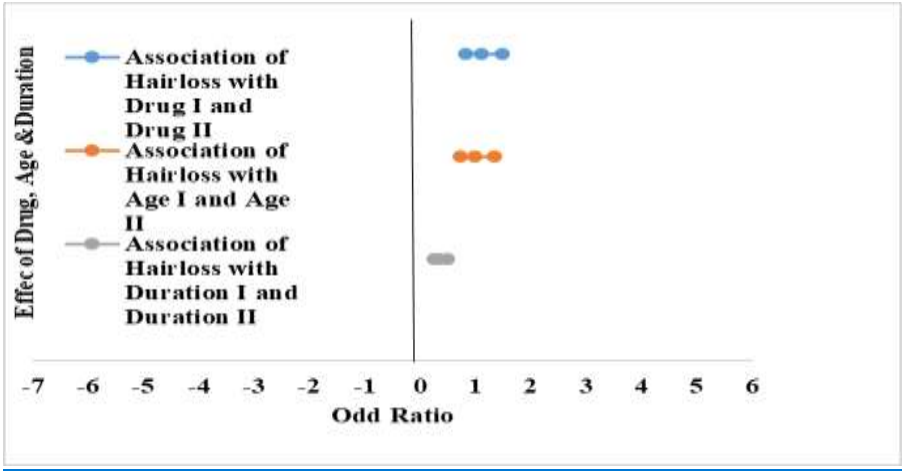

Figure 3: Association of Hair loss with Drug, Age and Duration

Conversely, in the given number of cases, weight gain was found to be more associated with Drug-II than Drug-I, with 59.1% and 40.9% of cases, respectively (Table 07). A statistically significant association of weight gain was observed with Drug-II (chi-square value=12.53 and p=0.0001) compared to Drug-I. The odds of weight gain with Drug-II were 2.36 times greater than with Drug-I, with a 95% CI ranging from 1.14 to 1.79 (Table 08).

Table 7: Crosstab and Chi Square Test Of Combined Oral Contraceptive (COCs) Verses Depo –Provera For Weight Gain

EFFECT OF DRUGS		**WEIGHT GAIN**		**TOTAL**
		Weight gain Yes	Weight gain No	
COCs[a] (Drug-I)	Count	200	165	365
	% Weight gain	40.9%	53.7%	45.9%
Depo-Provera[b] (Drug-II)	Count	289	142	431
	% Weight gain	59.1%	46.3%	54.1%
Total	Count	489	307	796
	% Weight gain	100%	100%	100%
EFFECT OF AGE		**WEIGHT GAIN**		**TOTAL**
		Weight gain Yes	Weight gain No	
Age I (years) 19-35	Count	322	123	445
	% Weight gain	65.8%	40.1%	55.9%
Age II (years) 36-50	Count	167	184	351
	% Weight gain	34.2%	59.9%	44.1%

Total	Count	489	307	796
	% Weight gain	100%	100%	100%
EFFECT OF DURATION		**WEIGHT GAIN**		**TOTAL**
		Weight gain Yes	Weight gain No	
Duration I (6months-1 year)	Count	154	157	311
	% Weight gain	31.5%	51.1%	39.1%
Duration II (1-2 years)	Count	335	150	485
	% Weight gain	68.5%	48.9%	60.9%
Total	Count	489	307	796
	% Weight gain	100%	100%	100%

[a]Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b]Depro-Provers (Depotmedroxy progesterone acetate)

Table 8: Logistic Regression Predicting Weight Gain between Different Drugs, Age Group and Duration

Description	**DRUGS** **Drug-I (COCs[a]) & Drug-II (Depo-Provera[b])**		**AGE** **Age I(19-35)&Age II (36-50)**		**DURATION** **Duration I (6months-1 year) & Duration II (1-2 years))**	
Number of reported cases	796		796		796	
Omnibus Tests of Model Coefficient s	Chi-Square	*p*-value	Chi-Square[c]	*p*-value	Chi-Square	*p*-value
	12.53	0.0001	51.06	0.0001	30.43	0.0001
Variables in the Equation	Drugs verses Weight gain		Age verses Weight gain		Duration verses Weight gain	
	Odds Ratio (Exp β)	95% CI Lower - Upper	Odds Ratio (Exp β)	95% CI Lower – Upper	Odds Ratio (Exp β)	95% CI Lower - Upper
	2.36	1.14 – 1.79	2.88	2.14-3.87	1.431	0.776-1.371
p-Value	0.0001		0.0001		0.0001	

[a] Combined Oral Contraceptives (Levonorgestrol & Ethinyl estradiol)
[b]Depro-Provera (Depotmedroxy progesterone acetate)
[c] chi-square table value=3.84 (CI=95% and DF=1)

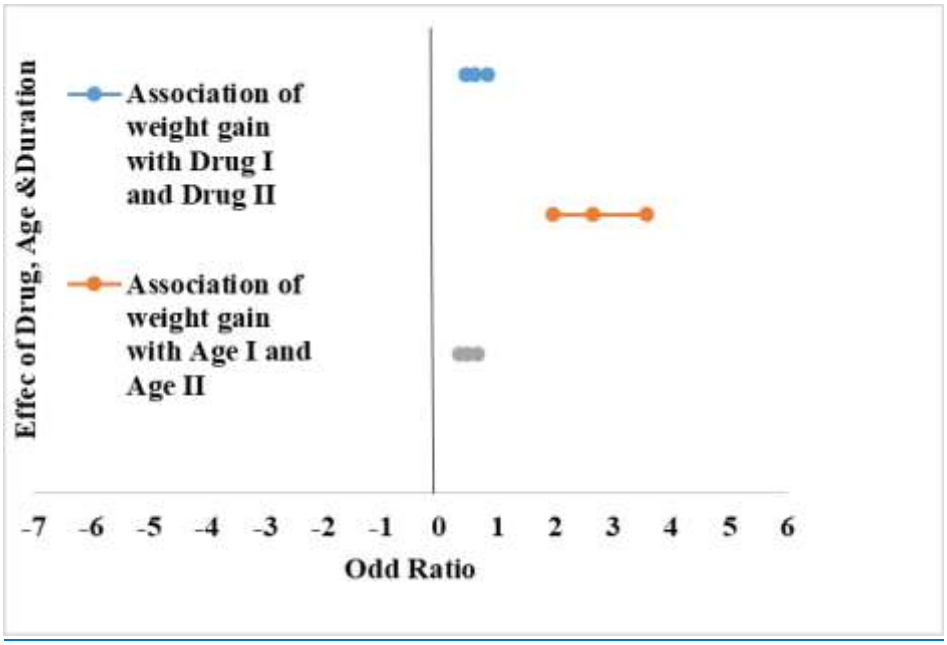

Figure 4: Association of Weight Gain with Drug, Age and Duration

Association of Side effects with Age I and Age II:

Upon evaluating the specified age groups for the occurrence of side effects linked with Drug-I and Drug-II, the Omnibus test revealed a significant association of nausea, vomiting, and weight gain ($p < 0.05$), except for hair loss.

In Age I (n=441), 219 out of 364 cases (60.2%) and in Age II (n=355), 145 out of 364 cases (39.8%) were reported for nausea (Table 01). The odds ratio (OR) for nausea in Age I compared to Age II was 1.429 at a 95% confidence interval (CI) of 1.077-1.895, with a chi-square value of 1.673 (p=0.01) (Table 02).

For vomiting, the occurrence was 62.2% in Age I and 37.8% in Age II (Table 05). The chi-square value was 6.89 (p=0.0009), with an OR of 1.462 at a 95% CI of 1.100-1.942, indicating a stronger association with Age I than Age II (Table 06).

Similarly, in the assessment of weight gain, 65.8% of cases were reported in Age I and 34.2% in Age II (Table 04). The Omnibus test showed a chi-square value of 51.06 (p=0.0001) (Table 07). The OR indicated that the odds of weight gain in Age I were 2.8 times greater than in Age II, with a 95% CI of 2.14-3.87.

However, when comparing the likelihood of hair loss between Ages I (54.2%) and Age II (45.8%), cases were observed (Table 05). The OR values indicated that hair loss was 1.532 times more likely in Age II than in Age I, with a 95% CI of 0.776-1.371 and a chi-square value of 0.046. However, the p-value of 0.830 (>0.05) indicated an insignificant association of hair loss with Age I.

Association of Side effects with Duration I and Duration II:

The duration of contraceptive use significantly influences the occurrence of side effects. In the current study, 246 out of 364 cases (72.5%) and 100 out of 364 cases (27.5%) of nausea were reported among women using selected contraceptives for Duration I (less than 1 year) and Duration II (1-2 years), respectively. The chi-square test yielded a value of 3.64 (p=0.0001). Nausea was found to be 3.59 times more associated with Duration I than Duration II, with a 95% confidence interval of 2.66-4.84 (Table 02).

For vomiting, 263 out of 360 cases (73.1%) and 97 out of 360 cases (26.9%) were observed in Duration I and Duration II, respectively (360 being the total number of cases with "yes" responses in each duration). The chi-square value was 65.19 (p=0.0001) (Table 03 and 04). The estimated odds ratio (OR) indicated that the odds of vomiting for Duration I were 3.32 times greater than for Duration II, with a 95% confidence interval of 2.46-4.48.

However, the presence of hair loss was reported in 27% of cases for Duration I and 73% for Duration II (Table 05). An insignificant association of hair loss was observed with Duration I (chi-square= 4.62; p=0.60) (Table 06), with an OR of 1.033 at a 95% confidence interval of 0.776-1.371.

Similarly, when examining the occurrence of weight gain, 31.5% and 68.5% of cases were found, respectively. A statistically significant association of weight gain was noted with Duration II, with a chi-square value of 30.34 (p=0.0001). The odds of weight gain were 1.431 times higher for Duration II than for Duration I (CI=95%, 0.776-1.371) (Table 08).

2. DISCUSSION:

Based on the review of existing literature, this study represents the inaugural investigation aimed at assessing the occurrence and correlation of minor side effects associated with Levonorgestrel & Ethinyl estradiol (COCs) and Depotmedroxyprogesterone acetate (Depo-Provera) concerning age and duration of use within governmental birth control centers in Pakistan. Comparable studies have been undertaken by various researchers in diverse geographic regions across the globe, as noted by Archer et al [20] reported that in United States women taking depot medroxy progesterone acetate for birth control experienced, hair loss, and weight gain. In the current study weight gain was found more associated with the use of Depotmedroxy progesterone acetate but hair loss with Levonorgestrol & Ethinyl estradiol. Similarly Dal'Ava, N. et al [21] when compared Depotmedroxy progesterone acetatewith copper intrauterine device (IUD), prevalence of weight gain was found more with Depotmedroxy progesterone acetatewithin the first year of use that might be due to its potential to increase fat mass. The present study revealed that weight gain was more observed in Age I (19-35). A study by Beksinska et al also reported that weight gain due to the use of injectable hormonal contraceptives was found more in early age group i.e. 15-19, than combined oral contraceptives user [22]. Hani, D. et al also described that weight gain is one of the commonly reported side effect associated with the use of hormonal contraception and reported that during use of hormonal contraceptives, weight fluctuates by 3 kg approximately over an observation interval from 6 to 24 months [23].

Some researchers have also investigated other untoward outcomes produced by the hormone replacement therapies used for contraception. Beksinska, M. E. et al reported that the use of depot-medroxyprogesterone acetate (DMPA), norethisterone enanthate (NET-EN) and low-dose combined oral contraceptives (COCs) has been associated with loss of bone mineral density (BMD)

in young women (aged 19-24 years) and BMD was found lower due to long-term injectable use but not with mixed injectable and COC use [24]. Berenson et al evaluated the effect of injectable and oral contraceptives on glucose and insulin levels on every 6 months thereafter for 3 years and concluded that the use of depot medroxyprogesterone acetate can produce slightly higher fasting glucose and insulin levels [25]. Ahrendt et al while working on efficacy, acceptability and tolerability of different methods of contraception, concluded that estrogen-related untoward outcomes like breast pain and nausea were the most common reasons for abrupt withdrawal of combined oral contraceptives [26].

3. CONCLUSION:

The research findings suggest that nausea, vomiting, weight gain, and hair loss may significantly contribute to noncompliance with hormone replacement therapy for contraception, with potential dependence on age and duration of therapy. The presence of these adverse effects could lead to contraceptive failure. Further investigations are warranted to fully elucidate the significance of major side effects associated with these contraceptive agents.

Compliance with Ethical Standards

Ethical Approvals:

It was a retrospective, cohort, non-interventional, observational, study of 1149 women, and was conducted according to declaration of Helsinki, after the approval of Ethical review board of Jinnah University for Women. The women were enrolled after verbal consent.

Conflict of Interest:

All authors involved in this study are esteemed academicians and researchers. Ms. Huma Dilshad, the primary author, is a PhD scholar in the Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi. Dr. Rabia Ismail Yousuf, serving as the second author, holds the position of research supervisor, while Dr. Muhammad Harris Shoaib, the third author, also offered research guidance. Both Dr. Yousuf and Dr. Shoaib are dedicated full-time teaching faculty members in the Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi.

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Author Contributions:

All authors participated fully throughout the study period. The concept of the study was proposed by Ms. Huma Dilshad, a PhD scholar, contributed in data collection and literature survey. Dr. Rabia Ismail Yousuf, the research project supervisor and Dr. Muhammad Harris Shoaib, provided guidance in data analysis and interpretation.

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