

Influence of Combined Oral Contraceptives on the Onset of Cervical Intraepithelial Neoplasia.

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SUMMARY

The study focuses on the effects of combined oral contraceptives (COCs) on the onset of cervical dysplasia among Zimbabwean women. Women who had used COCs for at least 2 years and were in continued use were compared to non-users of COCs (control group). It was difficult to establish the average period of contraceptive use because in most instances there was no proper documentation on the exact dates as to when the subjects started using COCs. The number of subjects with each condition was noted from each of the following age groups ;<20 years, 20-29years, 30-39years, 40-49years and >50years. It was found that the percentage of the control group with benign conditions was higher than that of COC users in all age groups. Significant differences at 95 percent confidence level were noted for the 20-29 years age group ($z = -2.21$) and 40-49 years age group ($z = -2.53$). The number of subjects in the <20 years and >50 years age groups were too small for z-score computation. No significant differences were noted for mild to moderate cervical inflammation in all age groups. There was a higher percentage of COC users with severe cervical inflammation compared to the control group in all age groups. Significant differences were noted in the 30-39 years age group ($z = 3.45$) and 40 - 49 years age group ($z = 1.98$). A higher percentage of CIN I was noted among pooled COC users compared to the control group ($z = 2.00$) although no significant differences were obtained within different age groups. In conclusion, severe cervical inflammation and CIN I are more frequent among Zimbabwean women who use COCs as compared to non-users of COCs. Frequencies of advanced CIN are low among women who undergo routine cytological screening because this enables early detection and subsequent treatment.

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Introduction

Dysplasia or cervical intraepithelial neoplasia (CIN) refers to disordered growth development of epithelial lining of the cervix. Prevalence figures for cervical dysplasia vary from 1 to about 4 percent in non pregnant patients [1-4]. The varying degrees of dysplasia represent a continuum in cervical deterioration with advanced conditions leading to metastatic cervical cancer [1,5,6].

Although the causes of most cancers remain unknown recent research has led to advances in understanding the mechanism of malignant cell proliferation. The abnormal proliferation of cancerous cells has been linked to increased expression of protooncogenes. Alternatively this may result from a deletion of tumour suppressor genes [1,7]. Recent studies have also provided strong evidence that certain strains of Human Papillomaviruses (HPVs) are the

prime etiologic suspects that cause premalignant changes in cervical cells [8,9,10,11].

A number of studies have been carried out to investigate other risk factors associated with CIN and cervical cancer including smoking, sexual activity, obstetric and gynaecological history and use of combined oral contraceptives. Most of these probably are proxies for HPV infection [6,9,11 – 13]. Although several studies have shown that prolonged use of oral contraceptives reduces the risk of ovarian and endometrial cancer [14 –18], there are possibilities that combined oral contraceptives (COCs) maybe carcinogenic to the cervix [19,20]. It has been difficult to establish an actual cause – and – effect relationship that explains recent observations of an increase in cervical cancer risk for long – term oral contraceptive users [18].

Worldwide, an estimated 8 percent of all married women in Costa Rica, Morocco and Zimbabwe have used the pill at some point. In Bolivia, Colombia, The Dominican Republic, Guatemala, Nicaragua and Zimbabwe, between 50 and 60 percent of sexually active unmarried women have used the pill [18]. In Zimbabwe, access to the pill has been described as very good compared to other developing countries [21]. The Zimbabwe National Family Planning Council (ZNFPC) distributes a number of contraceptives at public sector facilities such as municipal clinics, rural district council clinics, ZNFPC Clinics and Ministry of Health and Child Welfare Hospitals and Rural Health centres. The distributed contraceptives include condoms, diaphragms, foams, progestin only pills, COCs, intrauterine devices and injectables [22].

Cervical cancer accounts for 231 000 annual deaths worldwide, 80 percent of which are in developing countries. Rates are highest in Melanesia, Southern and Eastern Africa and Central America [23,24]. Most of the malignant, conditions are amenable to intervention either at preventive level or by

screening [7,25]. For example even one cervical Papanicolaou (PAP) smear in a woman's lifetime, has been shown to reduce the incidence of cancer of the cervix by up to 26 percent [25,26]. As such it is important to ascertain some proxies for malignant carcinomas such as the cervical one so that metastasis maybe controlled at an early stage.

Although use of COCs is high in Zimbabwe, statistical significance tests of the relationship between use of COCs and development of CIN have been poorly documented. This study was carried out to assess the relationship between use of COCs and the onset of cervical dysplasia among Zimbabwean women.

Materials and Methods

Subjects

A total of 362 women aged 16 – 60 years (average age 33,02years) who visited the ZNFPC clinics in Bulawayo and Gweru , Zimbabwe during the period June 2000 to December 2001 were considered in this study. Of these 175 had a history of using COCs for at least 2 years although in most instances the exact periods were not documented. The other 187 women from ZNFPC clinics used alternative forms of contraception other than COCs and these constituted the control group.

Specimen Collection and Processing

Smears were collected from the squamocolumnar junction using the Aylesbury spatula by specialised personnel from ZNFPC clinics in Gweru and Bulawayo, Zimbabwe. These were then analysed at Mpilo Hospital Cytological Laboratories using the Auto PAP automated cytology screening system. Each smear was classified according to the extent of dysplasia which fell in one of the following categories: Benign, Benign with mild to moderate inflammation, severe inflammation, CIN I and CIN II.

Analysis of Results

For each class of dysplasia, subjects presenting themselves at the ZNFPC clinics were classified as users of COCs and non-users of COCs (control group). The number of subjects with each condition was noted from each of the following age groups: < 20 years, 20 – 29 years, 30 –39 years, 40-49 years and >50 years. The proportion of women with a given condition from the users of COCs was compared to that of the control group in percentages for each age group and the pooled sample. The null hypothesis was examined using the z - score [27].

The study was approved by the Mpilo Hospital Ethical Research Committee, Gweru General Hospital Ethical Research Committee, the Zimbabwe National Family Planning Council and the Research Board of the National University of Science and Technology, Zimbabwe. The study was funded by the Michael Gelfand Medical Research Foundation, Zimbabwe.

Results

From a total of 362 women presenting themselves at the ZNFPC clinics 175 of them were on continual COC use for at least

2 years. The other 187 women constituted the control group. From the sample only 4 women were below the age of 20. This figure was too small for z- score computation. The same applied for the 12 women over the age of 50 years. In the 20 – 29 years age group a total of 127 women were sampled, 52 of whom were COC users and the other 75 belonged to the control group. Of the 163 women in the 30-39 years age group, 95 of them were COC users and 68 were from the control group. Of the 56 women in the 40 – 49 years age group, 24 were COC users and 32 were a control group.

Tables 1 to 5 depict the percentages of women with different conditions of dysplasia by age groups for the experiment and control groups. Z – scores were determined at 95 percent confidence level ($z_c = 1.96$). The total number of COC users in each age group is represented by n_1 and the number of non users of COCs (control) is represented by n_2 . The sum of subjects in each age group is n . The percentage of COC users with a given condition of dysplasia is given by p_1 and that of the corresponding control sample by p_2 . Asterisks indicate samples too small for z- score computation.

Table 1: statistical distribution of women with a Benign condition from family planning clinics

Age Group (Years)	n	n_1	n_2	No. from n_1 with condition	No. from n_2 with condition	p_1	p_2	z score
< 20	4	0	4	0	3	0,00	75	*
20 -29	127	52	75	23	48	44,23	64,00	-2.21
30 -39	163	95	68	39	38	41,05	55,88	-1.87
40-49	56	24	32	10	24	41,67	75,00	-2.53
50+	12	4	8	3	4	75,00	50,00	*
Pooled sample	362	175	187	75	117	42,86	62,57	-3,57

Table 2: statistical distribution of women with mild to moderate cervical Inflammation from family planning clinics.

Age Group (Years)	n	n ₁	n ₂	No. from n ₁ with condition	No. from n ₂ with condition	p ₁	p ₂	z score
<20	4	0	4	0	1	0.00	25.00	*
20-29	127	52	75	16	20	30.77	26.67	0.50
30-39	163	95	68	22	23	23.16	33.82	- 1.50
40-49	56	24	32	7	6	12.15	18.75	0.91
50 ⁺	12	4	8	0	3	0.00	37.50	*
Pooled Sample	362	175	187	45	53	25.71	28.34	-0.56

Table 3: Statistical distribution of women with severe Inflammation from family planning clinics .

Age Group (Years)	n	n ₁	n ₂	No. from n ₁ with condition	No. from n ₂ with condition	P ₁	p ₂	Z score
< 20	4	0	4	0	0	0.00	0.00	*
20 –29	127	52	75	11	7	21.15	9.33	1.88
30 –39	163	95	68	30	6	31.58	8.82	3.45
40-49	56	24	32	6	2	25.00	6.25	1.98
50 ⁺	12	4	8	1	1	25.00	12.50	*
Pooled Sample	362	175	187	48	16	27.43	8.56	4.70

Table 4:Statistical distribution of women with CIN I from family planning clinics.

Age Group (Years)	N	n ₁	n ₂	No. from n ₁ with condition	No. from n ₂ with Condition	p ₁	p ₂	z score
< 20	4	0	4	0	0	0.00	0.00	*
20 -29	127	52	75	2	0	3.85	0.00	1.71
30 -39	163	95	68	4	1	4.21	1.47	0.37
40-49	56	24	32	0	0	0.00	0.00	0.00
50 ⁺	12	4	8	0	0	0.00	0.00	*
Pooled sample	362	175	187	6	1	3,43	0,53	2.00

Table 5: Statistical distribution of women with CIN (II) from family planning clinics

Age Group (years)	N	n ₁	n ₂	No. from n ₁ with condition	No. from n ₂ Condition	p ₁	p ₂	Z score
<20	4	0	4	0	0	0.00	0.00	*
20-29	127	52	75	0	0	0.00	0.00	0.00
30-39	163	95	68	0	0	0.00	0.00	0.00
40-49	56	24	32	1	0	4.17	0.00	1.17
50+	12	4	8	0	0	0.00	0.00	*
Pooled sample	362	175	187	1	0	0.57	0.00	0.72

Table 1 depicts the statistical distribution of women with benign conditions of cervical dysplasia for all age groups. The percentage of the control groups with benign conditions is higher than that of COC users for all age groups. The z values were not computed for the <20 years and > 50 years age groups because the samples were too small. Significant differences were noted for the 20 –29 years age group ($z = -2.21$), 40 – 49 years age group ($z = -2.53$) and the pooled sample ($z = -3.75$). There is no significant difference in the 30 – 39 years age group.

The distribution of women with mild to moderate cervical inflammation is shown in Table 2. With the exception of the <20 years and > 50 years age groups where the samples are small, there is no significant difference in all other age groups with regard to mild to moderate inflammation incidences. The overall z value for the pooled sample is -0.56 .

The general trend shows a higher percentage of COC users with severe cervical inflammation compared to non-users of COCs as shown Table 3. There is no significant difference in the 20-29 years age group ($z = 1.88$). Significant differences were noted for the 30-39 years age group ($z = 3.45$), 40 –49 age group ($z = 1.98$) and for the pooled samples ($z = 4.7$).

Table 4 depicts the distribution of women with CIN I by age groups. Although no significant differences were noted for all age groups, there is a significant difference

for the pooled sample ($z = 2.00$). Fewer women have this condition compared to other cervical dysplasia conditions. There were 2 cases identified in the 20 –29 years age group and 4 cases in the 30 –39 years age group.

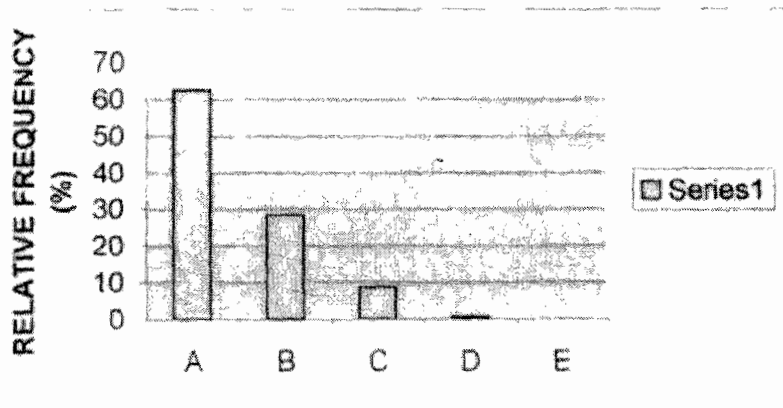
From table 5, only one case of CIN II was identified in the 40-49 years age group. No significant differences were noted in all age groups because of the limited cases observed.

The overall graphical presentation for the distribution of all cervical dysplasia conditions for control group and users of COCs are shown in Figure1 and Figure 2 respectively.

Discussion

This study has demonstrated that very few women below the age of 20 years visit the ZNFPC clinics. This could be attributed to the stigma associated with reproductive health issues. Most tribes in Zimbabwe do not encourage involvement in reproductive issues before marriage [28]. According to the Zimbabwean law, the legal age of majority is 18 years, after which a child may assume freedom of association and choice other than that dictated by her parents. Most women get married after this age hence they can now consult gynaecologists and family planning clinics for advice. Dysplasia has however been shown to occur in females aged 15years and older, with a peak

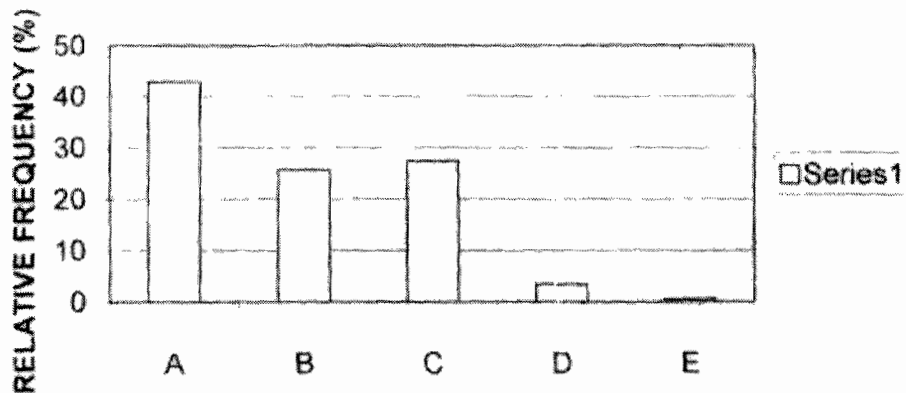
FIG 1. Distribution of the Relative Frequency of Cervical Dysplasia in control women.



key

- A - Women with benign dysplasia
- B - Women with mild to moderate cervical inflammation
- C - Women with severe cervical inflammation
- D - Women with CIN I
- E - Women with CIN II

FIGURE 2 : Distribution of the relative frequency of cervical dysplasia in coc users.



key

- A - Women with benign dysplasia
- B - Women with mild to moderate cervical inflammation
- C - Women with severe cervical inflammation
- D - Women with CIN I
- E - Women with CIN II

incidence in the age group 25 to 35 years [1,5]. In this regard it is therefore necessary to infer the etiological incidences of cervical intraepithelial neoplasia among Zimbabweans within 1 year post menarche as recommended by Stirrat [1]. For this to be achieved, there is need for an integrated health education for the parents.

The study also demonstrated that higher percentages of women from the non users of COCs had benign dysplasia conditions compared to COC users. This trend was observed for all age groups with significant differences recorded for the 20-29 years, 40-49 years and the pooled sample. This suggests that non -contraceptive users are at a reduced risk of metabolic processes that stimulate cellular inflammation of the cervix compared to COC users. No significant differences were observed in all age groups with regard to women with mild to moderate cervical inflammation.

The study revealed that use of COCs could be responsible for precipitating severe inflammation in all age groups as shown in Table 3. COCs contain estrogen and progestins both of which theoretically have the potential to cause cervical ectopy, a condition in which a specific type of cell that lines the inside of the cervical canal extends onto the outer surface of the cervix [29]. This is probably one mechanism in which inflammatory changes occur in COC users. Alternatively cervical ectopy may in turn increase vulnerability to some sexually transmitted infections such as chlamydial and gonococcal infections [30], possibly resulting in cervical inflammation. Research has shown that oral contraceptive users are more likely to become infected with chlamydia than non users, although the mechanism by which this happens is still unclear [29,31].

The study has also revealed a higher percentage of COC users with CIN I as compared to non users of COCs. However no significant differences were observed within the different age groups although the difference was significant for the pooled sample. These results are supported by

Tierney et al [2] who state that COCs are among the proxies for HPV infection which is the primary cause of cervical neoplasia and cancer [32].

It is interesting to note that there was only one case of CIN II in the whole sample. Since all women were drawn from ZNFPC clinics it follows that most of them undergo regular cytological screening. This study has therefore revealed that cytological screening has contributed to the prevention of acute cervical infections among Zimbabwean women who use the ZNFPC clinics. Cytological screening has been shown to reduce the risk of acute infection by about 26 percent [1,33]. This also explains why no cases of CIN III were observed among women who visit ZNFPC clinics.

As shown in figure 1, this research demonstrated a general trend in which benign conditions of cervical dysplasia were more frequent among non -users of COCs compared to COC users. No significant difference was shown for mild to moderate cervical inflammation between the 2 groups. Incidences of severe inflammation and CIN I were more frequent among COC users than non - users.

The study has some methodological biases which may have influenced the results. Since the sample was drawn from urban cities these observations only depict the situation that prevails among urban woman who have regular cytological screening. The situation maybe different for rural women, most of whom have been shown to be ignorant about the possible health hazards posed by CIN and cervical cancer [28]. This explains the need to establish a rural based reproductive health education programme for women to appreciate the need for cytological screening. However progress may also be hampered by the limited cytology screening laboratories in Zimbabwe. There are only two public health laboratories that screen CIN at affordable rates. These are located in the two major cities, hence depriving rural women of the privilege to have accessible screening facilities.

We may therefore justifiably speculate the possibilities of higher incidences of CIN in rural women where early symptoms of dysplasia may not be identified hence no corrective measures taken.

Although all COC users that were sampled had used oral contraceptives for at least 2 years, in most cases no documentation was available to indicate the exact date when the subjects started using COCs. This made it impossible for the researchers to correlate incidences of CIN to the period of COCs use among Zimbabwean women.

Conclusion

In conclusion severe cervical inflammation and CIN I are more frequent among Zimbabwean women who use COCs as compared to non- users of COCs. Frequencies of advanced CIN are low among women who undergo routine cytological screening because this enables early detection and subsequent treatment.

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