

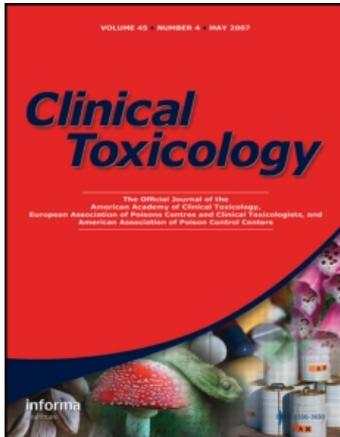
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ARTICLE

# Assessment of short-term outcomes following unintentional ingestions of “oral contraceptive pills” by toddlers

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**Background.** Cases of unintentional pediatric ingestions of oral contraceptive pills are commonly reported to Poison Information Centers (PICs). No study had examined clinical outcomes in the past 30 years, although the hormone content of these preparations has been substantially reduced. We assessed short-term outcomes to determine the relevance of advice provided, particularly that vaginal bleeding can occur. **Methods.** Prospective observational study of cases reported to a state PIC were followed up over a 5-month period. **Results.** There were 63 cases with complete follow-up, average age was 2 years and 10 months; 65% of the patients were female. Median number of pills ingested was 5.0 [Interquartile Range (IQR) 3–16.5]. Minor symptoms including vomiting and irritability were reported in 44% of cases. No case of vaginal bleeding was reported. **Conclusion.** No major clinical effects and no instances of vaginal bleeding were reported.

**Keywords** Acute poisoning; Pediatric; Poisoning; Poison control centers; Poisoning management

## Introduction

Unintentional ingestions of oral contraceptive pills by children are common events in Australian homes and a cause of anxiety for parents. The Western Australian Poisons Information Centre (WAPIC) handles on average 340 such cases per year from a service population of approximately four million. Across Australia, each year an estimated 2,000 cases are reported to Poison Information Centres (PICs).

Currently, the advice provided to parents at the time of consultation by all four Australian PICs is that such exposures have no long-term consequences but may produce minor, self-limited clinical effects (1–8) such as mild nausea and vomiting within 15 h of ingestion (2,3), drowsiness (2), headache (7), and vaginal bleeding 1–3 days later (5–8). Parents are advised that such symptoms can be managed at home without the need for decontamination or medical referral. This advice is based on reports published in the 1960s and 1970s (1–4) at a time when oral contraceptive pills contained much higher amounts of estrogens and progestins (9).

Enovid<sup>®</sup>, the first combined oral contraceptive marketed in the United States, was released as a contraceptive agent in 1960 (9). Each pill contained 150 µg of synthetic estrogen and 10 mg of synthetic progestin (9). Today, over 30 different

oral contraceptive pill preparations are commercially available in Australia. These contain 30–50 µg of ethinylestradiol and 50–1,000 µg of synthetic progestins. The small quantities of hormone in each pill and their rapid clearance rates (10) support the classification of these preparations as minimally toxic.

The combined oral contraceptive pills of today contain less estrogen and less progestins than the first pills, but the ill effects of unintentional pediatric ingestions of the current preparations are unknown. In particular, vaginal bleeding is based on one unsubstantiated report (8) published more than 20 years ago and has been widely reported in subsequent reviews (5–7). The purpose of this study is to determine short-term outcomes from unintentional ingestions of oral contraceptive pills by toddlers.

## Methods

This was a prospective observational study involving continuous recruitment of cases reported to the WAPIC from June through October 2003. At the time of the initial phone conversation, case details were recorded directly to the International Program on Chemical Safety Data Management System. Relevant details included time and date of exposure, patient age and gender, product name, estimated number of pills ingested, type of pills ingested, co-ingestants, the presence of any clinical features, severity, and treatments carried out.

Ethics approval for the study was obtained from the Clinical Audit Committee at Sir Charles Gairdner Hospital, Western

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Australia. Verbal consent for follow-up calls was obtained from the parent at the time of the initial phone consultation.

Cases were included if the patient was 12–60 months old at the time of the call and the care-giver reported suspected ingestion of one or more oral contraceptive pills. Cases were excluded if there were co-ingestants, if the child was suffering from any acute illness (febrile condition, gastroenteritis, and upper respiratory tract infections) or chronic medical conditions, and if the first communication to the WAPIC took place more than 12 h post-ingestion. Cases involving ingestion of sugar pills only were excluded.

Follow-up calls were made 3–11 days later to confirm exposure details and the presence of co-existing medical conditions to determine short-term outcomes and to gather more details of the exposure. Confirmation of the brand name and the number and types of pills ingested was made. Clinical features, time of onset and severity, and treatments were recorded. Severity was graded by the Poisons Severity Score (11).

Descriptive analysis was carried out using SPSS Version 13.0 for Windows. Values were expressed as mean  $\pm$  SD. Estimated total progesterone and total estrogen dose were calculated for each exposure. The presence or absence of clinical features was compared with the total dose of estrogens and progestins. When the number of ingested tablets was uncertain, the mid-point of the range was taken. In cases where two siblings shared tablets, each was allocated half the total amount.

## Results

Over the 5-month study period, 157 cases met inclusion criteria. Of these 113 (72%) agreed to follow-up. Of the 113 cases where agreement for follow-up was obtained, 33 (29.2%) were lost because of unsuccessful contact, eight (7.1%) were excluded because of pre-existing medical conditions, seven (6.2%) were outside selection criteria for age and time of call, and two (1.8%) were excluded because of pills being subsequently found.

Of the remaining 63 cases, 41 (65.1%) of the patients were female and 22 (34.9%) were male. Average age was 2 years and 10 months ( $33.5 \pm 10.2$  months, range 14–57 months). Average age of females was  $32 \pm 10.3$  months and  $36.2 \pm 9.8$  months for males.

Ingestions were reported to the PIC within 10 min (median) of the exposure [Interquartile Range (IQR) 5–40,  $n = 61$ ]. Sixteen different brand preparations were involved, three of which were progesterone-only preparations. In all but three cases the exposure occurred in the home (two in an office and one in a car). In 56 cases (88.9%) the child independently removed the pills from the blister pack. In two cases an older sibling shared and distributed the tablets and in five cases the access was not recorded.

Follow-up calls were made 3–11 days later (median 5.0, IQR 5–6,  $n = 63$ ). All follow-up calls in cases where the patient was female were made at least 4 days later (maximum

9 days). The median number of total pills ingested was 5.0 (IQR 3–16.5,  $n = 63$ , range 1–98). The median number of active hormone containing pills ingested was 4.0 (IQR 2–10.5,  $n = 63$ , range 1–77). Twelve cases involved ingestion of progesterone-only pills.

The mean estimated dose of synthetic progestin was  $2,017 \pm 5,189 \mu\text{g}$  ( $n = 63$ , range 30–34,000  $\mu\text{g}$ , median 600  $\mu\text{g}$ , IQR 175–1,650  $\mu\text{g}$ ). The only form of synthetic estrogen present in any preparation was ethinylestradiol. Ethinylestradiol was ingested in 51 cases, the mean dose was  $288.1 \pm 357 \mu\text{g}$  (range 30–2,310  $\mu\text{g}$ , median 150  $\mu\text{g}$ , IQR 88.9–413.5).

Clinical features were reported in 28 cases (44.4%) of all cases (51.2% of females and 32% of males). The median ingested dose of estrogen was similar for both: females 140  $\mu\text{g}$  (IQR 73.8–461,  $n = 41$ ), males 180  $\mu\text{g}$  (IQR 90–359,  $n = 20$ ). In all cases the clinical severity was graded as minor (11). Vomiting was reported in 14 cases, dry retching in one, and irritability in seven cases (Table 1). The average dose of synthetic estrogen at which vomiting was reported was  $265.3 \pm 185 \mu\text{g}$ , median 175  $\mu\text{g}$ , IQR 120–368.8,  $n = 14$ ). The lowest calculated dose at which vomiting was reported was 87.5  $\mu\text{g}$ . There were nine cases in which the child was reported to have ingested a month's supply or more. Clinical features were reported in only four of these nine cases. In one case the child was reported to be lethargic, in two cases vomiting, and in one case dry retching. Clinical effects were reported in three cases in which progesterone-only pills were ingested (in two cases irritability and in one case diarrhea). No episodes of vomiting or dry retching were reported in cases of ingestion of progesterone-only pills.

The time of onset of clinical features was recorded in 20 cases. Median time to feature presentation was 10 h, IQR 6–14 (range 5–48 h) (Table 1). Not a single case of vaginal bleeding was reported.

## Discussion

Over a 5-month study period 157 cases of unintentional ingestion of oral contraceptive pills by toddlers were reported to the WAPIC. In almost 90% of cases the toddler independently removed the pills from the blister pack. Patients were twice as likely to be female than male, which may reflect an association with gender-specific role-play. The calculated median steroid dose in this study was ethinylestradiol 150  $\mu\text{g}$  and progestin 600  $\mu\text{g}$ .

The clinical features reported here are consistent with previous studies (Table 2). Siferschmidt (2) reported symptoms in 20% of untreated pediatric cases, including vomiting within 15 h of ingestion. Punnonen and Salmi (12) reported headache and nausea in an adolescent female following the ingestion of 160 mg of estradiol valerate. However, some clinical features reported in this study are unlikely to be associated with pill ingestion (rash, cough, fever, and constipation).

An important finding of our study was that no instances of vaginal bleeding were identified. Traditionally, Australian

**Table 1.** Clinical features in relation to estimated ingested dose of synthetic estrogen

Clinical feature by organ system	Number of cases (n = 63)	Calculated ethinylestradiol dose, $\mu\text{g}$ (Mean $\pm$ SD)	Calculated ethinylestradiol dose range, $\mu\text{g}$	Time of onset (h) (median, IQR) <sup>a</sup>
<i>Gastro-intestinal</i>				
Vomiting	14	265.3 $\pm$ 185	87.5–630	10.0, 9–13 (n = 10)
Diarrhea	2	75 $\pm$ 106.1	0–150	12.5, 12.5–12.7 (n = 2)
Dry retching	1	2,310		NR
Abdominal pain	1	375		14 (n = 1)
Constipation	1	120		48 (n = 1)
<i>CNS</i>				
Irritability	7	337.5 $\pm$ 239.2	0–600	6, 6–10.5 (n = 6)
Drowsy/lethargy	2	292.5 $\pm$ 31.8	270–315	8.0 (n = 1)
Hyperactivity	1	140		NR
<i>Other</i>				
Cough	1	442		NR
Fever	1	120		NR
Rash	1	40		24
Vaginal bleeding <sup>b</sup> (subject n = 31)	0	254.8 $\pm$ 218.5	30–630	

NR, not recorded.

<sup>a</sup>The number of cases in which time of onset was recorded are in parenthesis.<sup>b</sup>Females only.**Table 2.** Reported clinical events by study

Year	Number of cases	Pill type	Clinical events (%)	Type of clinical events	Time to onset of clinical events (h)	Treatment
1962–1965 National Clearing House reported by Mofenson and Greensher	962	NR	4	Vomiting and nausea	NR	NR
1965 Francis and Dalzeil	9	Ortho-Novum <sup>®</sup>	0	None		Decontamination “in some”
1975 Silberschmidt	166	NR	20	Vomiting, nausea, and abdominal pain Occasional Apathy, drowsiness, epistaxis, facial swelling, swelling of external genitalia in a female	10–15	Decontamination
2008 Lynch, McKay and Murray	63	Combined pills of ethinylestradiol 30–50 $\mu\text{g}$ with synthetic progestins 50–1,000 $\mu\text{g}$	44	Vomiting and nausea, abdominal pain, drowsiness, and irritability	8–48	None

NR, not recorded.

PIC's have warned parents of the potential for endometrial proliferation and subsequent vaginal bleeding several days post-ingestion. This warning is likely to cause parental anxiety and may be interpreted by some parents as a reproductive insult. An extensive review of literature by one of the

authors failed to identify original case reports of vaginal bleeding. A reference to vaginal bleeding was first made by Francis and Dalzeil (1) who stated that “no instances of vaginal bleeding were identified” in their study of nine cases. Moeschlin (8) stated that “pseudomenstruation” can occur in

young girls following acute overdose, however, no case details are provided.

The only synthetic estrogen present in oral contraceptive pills preparations currently available in Australia is ethinylestradiol. This steroid is rapidly absorbed, with peak blood concentrations reported within 2 h and an elimination half-life of 19 h (13). Although the estrogenic dose required to cause uterine and endometrial mitotic responses in pre-school girls has not been established, animal and human studies suggest that repeated dosing at physiological or supra physiological levels over at least 48h is necessary to induce endometrial proliferation (14,15). It is therefore highly unlikely that a single dose of 150 µg of ethinylestradiol could induce endometrial proliferation in a toddler.

### Limitations

The limitations to this study are common to studies involving telephone reporting, recruitment, and follow-up. These include low recruitment numbers, inaccuracies in establishing dose, a reliance on unverified reporting, and possible inaccuracies in the care-givers recall of events several days after the event.

Of the 157 cases recruited in this study, only 63 cases had complete follow-up and of these 41 involved females, this combined with the relatively low study number means that uncommon clinical effects would not be identified. A much larger sample size would be required to establish whether vaginal bleeding occurs. It is also probable that the reported number of pills ingested is over estimated and that many of the pills that were unaccounted for had not actually been ingested by the toddlers.

### Conclusion

Unintentional ingestions of oral contraceptive pills by toddlers are common events in Australian homes as indicated by reports to PICs. Current advice provided by PICs includes a warning to expect minor short-term clinical effects, including nausea and vomiting and transient vaginal bleeding in young females. This advice is based on the studies conducted in the 1960s and 1970s when available preparations contained much higher doses of estrogens and progestins than now.

The findings of this study suggest that minor effects do occur in some children following ingestion of the currently

available oral contraceptive pill preparations. These effects are not of sufficient magnitude so as to warrant hospital referral. There were no reports of vaginal bleeding in this series and in the absence of any other data to support this complication occurring, it no longer seems appropriate to warn parents or care-givers that vaginal bleeding may occur.

### Acknowledgments

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