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Medroxyprogesterone Acetate Therapy in Early Pregnancy Has No Apparent Fetal Effects

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ABSTRACT Medroxyprogesterone acetate (MPA; Provera) was given orally to 449 women from the 5th to 7th week of pregnancy until at least the 18th week. Data are recorded from two treatment groups (recurrent abortion and threatened abortion) and are compared to a matched series. A total of 1,016 pregnancies are included in the study, and all patients were recruited from a subfertile population conceiving from a range of infertility treatments. Early pregnancy wastage was high throughout the groups and was significantly elevated (43%; $P < .001$) in those women who had vaginal bleeding in early pregnancy. The study focuses on the question of potential teratogenicity of progestagens administered in the first trimester. There were 15/366 (4.1%) infants with congenital abnormalities in the MPA-treated group and 15/428 in the untreated group (3.5%). The difference was not significant, and MPA is considered to have no embryopathic risk, nor is it likely to retain an abnormal fetus that might otherwise abort. It appears that MPA is a safe drug to use in pregnancy although the question of efficacy has not been addressed in this report. Considering other recent negative epidemiologic studies with regard to teratogenicity, we add to the conclusion that MPA cannot be demonstrated to have a measurable teratogenic risk and certainly does not present a risk for congenital heart disease and limb reduction defects.

The value of progestagen support therapy in the form of either progesterone or synthetic progestagens remains controversial (Shearman and Garrett, '63; Goldzieher, '64; Klopper and MacNaughton, '65; Jones et al., '74; Soules et al., '77; Fainstat and Bhat, '83; Tognoni et al., '83) as it has been shown that 50–60% of the fetuses obtained from women who experience spontaneous abortions have chromosomal abnormalities (Boue et al., '75; Simpson, '80). However, while the overall rate of spontaneous abortions is generally considered to be 10–15%, subfertile women who conceive following therapy appear more prone to abort their pregnancies. Approximately 20% abort following induction of ovulation with clomiphene citrate (MacGregor et al., '68; Murray and Osmond-Clark, '71), 29% following gonadotrophin injections (Lunenfeld and Insler, '78; Ben-Rafael et al., '81), 30–50% following in vitro fertilization (Trounson, '82; Yovich et al., '84; Seppala, '85), and up to 60% of those who conceive with antispermatozoal antibodies or following unexplained infertility (Jones, '76a). Habitual aborters can be shown to have abnormal ovulatory cycles categorized as luteal phase defects in 35% (Jones, '76b).

During the past 6 years, a large series of infertile couples has been managed at the PIVET Medical Centre, and recently we reported the pregnancy outcomes from a range of procedures involving ovarian stimulation and gamete manipulation including in vitro fertilization (IVF) techniques (Yovich and Matson, '88). We reported on 1,034 pregnancies in which the diagnosis was made at the time or within a few days of the due menstrual period. Early pregnancy

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wastage was 27%. This datum concurs with the findings of high fetal wastage following therapy in such patients (Jansen, '82). However, there is no clear explanation of the underlying causes of early pregnancy wastage in the subfertile population, as definitive studies to assess the chromosomes of aborted material in this group have not yet been reported. We suspect that a large proportion of such losses derive from causes other than fetal chromosome abnormalities. In an attempt to improve the pregnancy continuation rate in subfertile women, we have given progestagen support therapy using medroxyprogesterone acetate (MPA). Pure progesterone in a suitable therapeutic form such as a vaginal pessary or rectal suppository is not available in Australia; hence, MPA was chosen for its inexpensive availability and the fact that it can be administered orally. It was considered unlikely to produce fetal androgen effects as it is not a 19 nor-testosterone derivative, and a literature search revealed the absence of reported embryopathic effects in the human. This substituted progestagen has been shown to be a potent progestational agent with little or no estrogenic or androgenic properties (Greenblatt and Barfield, '59). Its effectiveness in maintaining pregnancies has been demonstrated in the rabbit (Wu, '61) and rat (Stucki and Glenn, '61) without untoward effects. MPA is considered to have 20–50 times the progestational activity of natural progesterone (Wu, '61; Stucki and Glenn, '61).

This report does not attempt to evaluate the efficacy of MPA therapy in the treatment of threatened or recurrent abortion but does focus on the question of teratogenicity. It contains a large population of patients exposed to relatively large doses of MPA throughout the period of fetal organogenesis. The report documents the outcome of 1,016 pregnancies from a total of 913 women, 449 of whom were treated with MPA because of indications of recurrent pregnancy losses or threatened abortion. A nontreated group was selected as a matched series for the purpose of assessing any effects of MPA on the infants who were exposed to the agent during the period of embryogenesis. Although a future report will focus on the efficacy of MPA, this study does examine the early pregnancy outcome in order to consider the additional question that progestagen support therapy might cause retention of an abnormal embryo that would otherwise have aborted.

MATERIALS AND METHODS

Patient selection

All patients were recruited from a larger population attending the PIVET Medical Centre for infertility management. The techniques of treatment have been well described with standard investigatory and treatment protocols (Yovich, '88). Infertility managements included ovarian stimulation, microsurgical tubal reconstruction, donor insemination, the intrauterine insemination of husband's washed sperm (AIH), in vitro fertilization-embryo transfer (IVF-ET), gamete intrafallopian transfer (GIFT), pronuclear stage tubal transfer (PROST), endometriosis therapy, and specific endocrinological treatments for conditions such as hyperandrogenism and hyperprolactinemia. Pregnancies were generally diagnosed in the 5th week after the last menstrual period and in all cases were examined soon after the diagnosis was made. Routine examination included a speculum examination of the vagina and cervix, undertaking vaginal and endocervical swabs (for aerobic, anaerobic, and chlamydial culture) and a repeat Papanicolaou smear if this had not been performed in the previous 12 months at the clinic. MPA was offered to women considered to be at increased risk of pregnancy loss because of recurrent abortions or because of bleeding causing an abortion before the 7th week. All patients were counseled and informed of the Burstein and Wasserman report ('64), which indicated that MPA did not cause major abnormalities but provided a potential risk for virilization of the female infant. The register was closed when the 508 treated patients and their matched controls had a known pregnancy outcome.

Recurrent abortion group (n = 199 pregnancies from 180 women): This series included women whose two previous pregnancies had aborted during the first trimester. It also included women who had a previous history of two or more pregnancy losses followed by a subsequent pregnancy that advanced whilst being treated with progestagens. Their ages ranged from 20 to 42 years with a mean of 31.1 ± 4.3 years.

Threatened abortion (n = 309 pregnancies from 269 women): This group comprised patients who presented with bright vaginal

bleeding sufficient to cause staining more than 3 cm on the underclothing. All patients were examined and advised to rest at home or admitted to hospital if the loss was of clinical concern. In all cases MPA therapy was commenced according to the schedule described below. The women's ages ranged from 22 to 44 years with a mean of 31.9 ± 4.1 years.

Matched series (n = 508 pregnancies from 464 women): As each case was selected for MPA therapy, another patient was drawn from the pool of pregnant patients achieved at the PIVET Medical Centre around the same time. They were matched as closely as possible for age (to within 2 years), background infertility problem, duration of infertility, and treatment method to achieve conception. Their ages ranged from 20 to 44 years with a mean of 31.2 ± 4.0 years.

The progestagen

Following informed consent, MPA (Provera tablets, 10 mg; Upjohn, Kalamazoo, MI) was administered to subfertile women with a history of recurrent spontaneous abortion or with threatened abortion. For recurrent aborters, treatment was initiated at the time of pregnancy diagnosis (usually day 16 of the luteal phase; designated 5th week), i.e., two tablets taken orally at 0600 h, 1200 h, 1800 h, and 2200 h, providing a total dose of 80 mg/day. For those with threatened abortion, the regimen used in the acute phase was two tablets given 4-hourly (0200 h, 0600 h, 1000 h, 1400 h, 1800 h, 2200 h), providing a total dose of 120 mg/day. As vaginal bleeding settled, the 0200 h dose was ceased, and 1 week later the regimen was converted to 20 mg q.i.d., the same dose received by the recurrent aborter group. In most cases the therapy was continued to 16 weeks gestation and then weaned slowly over the ensuing 2 weeks so that all treatment ceased by 18 weeks gestation. In ten patients considered to be at high risk because of recurrent bleeding or recurrent uterine irritability after reducing MPA, therapy was continued through 36 weeks gestation.

Pregnancy—diagnosis, terminology and monitoring

Pregnancy was diagnosed by an elevated serum β-hCG (human chorionic gonadotropin) level on or after day 16 of the luteal phase with a significant rise at least 3 days thereafter (Yovich et al., '86a). We utilize a β-hCG assay with minimum detection level of 2.5 IU/liter and consider a positive pregnancy diagnosis for all levels >25 IU/liter standardized against the second International Standard (IS 61/6). The serum estradiol (E2) and progesterone (P4) are measured in the same sample and are also required to be in the appropriate pregnancy range (>650 pmol/liter and >37 nmol/liter, respectively; Yovich et al., '86b). Patients were included in this study who had pregnancy diagnosed within 7 days of the missed menstrual period and had β-hCG, E2, and P4 measured weekly throughout the first trimester (Yovich et al., '85a; Yovich et al., '86b) until 12 weeks. Ultrasound assessment is performed in the 7th week. Pregnancies with falling hormonal levels that fail to reach the stage of a detectable gestational sac on ultrasound are known as biochemical pregnancies and are not submitted to uterine curettage. Pregnancies that reach the stage of a gestational sac at 7 weeks without a viable intrauterine fetus are regarded as blighted ovum pregnancies. Pregnancies aborting after ultrasonic detection of fetal heart movement are diagnosed as spontaneous miscarriages. Ectopic gestations are often diagnosed very early by the finding of elevated β-hCG, P4, and E2 levels but no definite intrauterine gestational sac on ultrasound performed in the 7th week. After 20 weeks gestation, fetal or neonatal demise is regarded as a late pregnancy loss, which is categorized into stillbirths, neonatal deaths (at any stage where the infant is not discharged from hospital), and total perinatal mortality (combined stillbirths and neonatal deaths).

Prenatal diagnostic/termination service

A routine service of amniocentesis was offered to all cases where maternal age was greater than 35 years or there were indications in either past or family history of chromosomal abnormalities or open neural defects. More recently, chorionic villus sampling using the transcervical method has been introduced in the prenatal diagnosis service. Patients are counseled before and after the procedures and can choose to terminate pregnancies where abnormalities are diagnosed.

Pediatric assessments

All the infants included were delivered at either King Edward Memorial Hospital for Women or St. John of God Hospital, which are the two main obstetric hospitals in Perth. They contain high-grade neonatal services provided by the one group of neonatal pediatricians. The duty-rostered member of the group examined all the infants at or soon after delivery. Infants with major abnormalities were further assessed by the geneticist. All infants were examined fully again at 6 weeks, and many have continued in long-term follow-up studies for the further evaluation of specific infertility treatments and MPA exposure (Yovich et al., '86c).

Statistics

Although the case selection includes paired sampling, this is only in respect to age, infertility background, and fertility treatment history. Therefore, data were compared using chi-square analysis in the appropriate contingency tables. The G statistic was calculated for the hypospadias observations using the log-likelihood ratio in contingency tables and applying Yates' correction (Zar, '74). The data were also examined as the ratio of a single Poisson variable to its expectation (Balar and Ederer, '64).

RESULTS

MPA was given to 449 women who had a total of 508 pregnancies (199 for recurrent abortion and 309 for threatened abortion). The same number of pregnancies (508) was selected into the matched series from 464 women who did not have MPA treatment. All pregnancies have a known outcome, either early (<20 weeks) or late (≥20 weeks).

Early pregnancy outcome

The early pregnancy outcome details are documented in Table 1. A significantly higher proportion of pregnancies was lost from the groups treated with MPA ($P < .001$), mainly arising from those women who presented with threatened abortion. Ectopic pregnancies were also more common in the group who presented with threatened abortion [29 cases (9.4%) compared with 5 (2.5%) in those with recurrent abortions and 29 (5.7%) in the untreated group]. Of the total early pregnancy wastage, the proportion of biochemical pregnancies, blighted ovum pregnancies, and ectopics was similar in the treated and untreated groups. However, there was a significantly lower proportion of spontaneous abortions in the treated groups. One of the recurrent abortion ectopics occurred in a woman who presented at 10 weeks gestation in severe shock with a heterotopic pregnancy. The intrauterine twins aborted spontaneously, subsequent to the salpingectomy operation. This case has been reported as part of a series of heterotopics (Yovich et al., '85b) and has been catalogued in the ectopic data. Two of the cases catalogued as threatened abortion leading to spontaneous abortion had previously had a chorionic villus biopsy at 8 weeks and subsequently developed proven intrauterine infections.

TABLE 1. Overall pregnancy outcome in women conceiving after infertility treatments

Total pregnancies		Early pregnancy wastage (<20 weeks)	Ongoing (≥20 weeks)
MPA-treated			
Recurrent abortions	199	57 (28.6)	142
Threatened abortions	309	133 (43.0)	176
Total	508	190 (37.4)	318
Untreated	508	132[1] (26.0)	376

[1]Includes seven terminations (three for genetic reasons, one for rubella vaccine innoculation, and three for psychosocial reasons). Values in parentheses are percentages.
*X^2 15.21, $P < .001$.

Late pregnancy outcome

Following the early pregnancy losses, there were 318 pregnancies proceeding beyond 20 weeks that had MPA exposure. There were fewer early pregnancy losses in the untreated group, and accordingly 376 pregnancies were ongoing beyond 20 weeks. Table 2 shows the multiple pregnancy distribution in the respective groups, and it can be seen that overall a total of 794 infants were delivered (366 following MPA exposure and 428 untreated controls). There were 188 males and 178 females in the MPA group and 214 of each sex in the untreated group. Therefore, there were no significant differences in the sex ratios from the treated and untreated groups. There was a higher perinatal mortality rate in the MPA-treated pregnancies, but the difference was not significant (Table 3). Specific details of each of

TABLE 2. Multiple pregnancy distribution in women conceiving after infertility treatments and proceeding beyond 20 weeks

	Total pregnancies	Type			Total infants
		Single-tons	Twins	Triplets	
MPA-treated					
Recurrent abortion	142	127	11	4	161
Threatened abortion	176	154	15	7	205
Total	318	281	26	11	366
Untreated	376	329	42	5	428
Total treated + untreated					794

TABLE 3. Late pregnancy outcome of infants whose mothers conceived after infertility treatments

		Perinatal mortality	Surviving infants
MPA-treated			
Recurrent abortion	161	10	151
Threatened abortion	205	9	196
Total	366	19	347
Untreated	428	14	414

the pregnancies resulting in perinatal mortality are shown in Table 4. There is a high proportion of spontaneous premature labor (both unexplained and related to multiple pregnancies) as the main cause of perinatal mortality amongst treated and untreated women.

Congenital abnormalities

Fifteen cases of congenital abnormality were documented in each of the treated and untreated groups (Table 5). This constituted 4.1% of MPA-exposed infants and 3.5% of unexposed infants. The difference is not significant. It should also be noted that four of the congenital anomalies were quite minor, all occurring in the MPA groups. The hydroceles regressed spontaneously in both cases and the two MPA-exposed males with hypospadias did not require surgery or prove of any concern to the parents. In both cases, the external urinary meatus is near the tip of the penis in the glans tissue. The case of hypospadias noted in the non-MPA-exposed group was more severe and did require surgery. There is no statistically significant difference in the hypospadias observations either between the two groups or when compared with other data recorded in the Western Australian Congenital Malformations Register (Bower and Stanley, '86), which reports the incidence as approximately 1/200 males. In the study data we noted two cases amongst 171 males exposed to MPA. Analysis of this datum showed the log-likelihood ratio to be insignificant ($G = 3.16$; $P > .05$).

Two of the MPA-exposed infants had fetal anomalies causing perinatal mortality. The infant with multiple abnormalities listed as thoracogastroschisis (Pagon et al., '79) had male chromosomes and displayed gastroschisis, absent right tibia and fibula with hypoplastic femur, horseshoe kidney, abnormal facies, hypoplastic lungs, an imperforate anus, and poorly developed male genitalia. The infant with several anomalies consistent with the diagnosis of Noonan's syndrome (Noonan and Ehmke, '63) was a male infant with normal XY karyotype. It had a broad neck with excess skin and a tendency to webbing, a low posterior hairline, low placed, large and overfolded ears, a broad chest with wide spaced nipples and pectus excavatum, kyphoscoliosis, short square hands and feet with hypoplastic nails, a slightly small jaw with a wide mouth, and hypertelorism. Autopsy revealed a congenitally abnormal heart with a hypoplastic left atrium and left ventricle and endocardial fibroelastosis of the left atrium. In addition, six lumbar vertebrae were noted, as well as an abnormally long descending colon, only two cord vessels and patchy neuronal loss in the cerebellum, considered to be secondary to hypoxia caused by congestive cardiac failure. In addition, a sacral dimple with an overlying tuft of hair was present.

The other congenital abnormalities associated with MPA exposure occurred in live infants that have thrived. The case of Goldenhar syndrome was one of triplet male infants arising following IVF. The case has been fully reported (Yovich et al., '85c), and the details of the infant are a deformed right pinna with microtia and, apart from the characteristics of wet hyaline membrane disease, a chest X-ray revealed two lumbar ribs and two thoracic hemivertibrae.

Klinefelter's syndrome occurred in the case of a 42-year old woman who achieved pregnancy by IVF. The condition was diagnosed at amniocentesis undertaken in the 16th week. However, following counseling and informed advice, the couple elected to continue the pregnancy. At delivery the male infant had normal features and has

TABLE 4. Perinatal mortality for pregnancies arising from infertility treatments[1]

Case No.	Gestation (weeks)	Cause	Autopsy
Matched group (no MPA exposure)			
1 and 2	31	PROM & spontaneous labor	Yes
3	32	IUGR	Yes
4	29	Spontaneous labor	No
5 and 6	24	Spontaneous labor, twins	No
7	35	IUGR	No
8	29	IUGR	No
9	39	Unexplained	Yes
10 and 11	24	Spontaneous labor, twins	No
12 and 13	25	Spontaneous labor, twins	No
14	24	Unexplained stillbirth	Yes

Case No.	Gestation (weeks)	Cause	Autopsy	MPA exposure (weeks)
Groups exposed to MPA				
1	23	Spontaneous labor	No	6–18
2 and 3	25	Spontaneous labor (twins)	No	6–18
4	28	Abruptio placentae and severe IUGR	Yes	5–28
5	25	Spontaneous labor	Yes	7–18
6	35	Multiple abnormalities (thoraco-gastroschisis)	Yes	7–18
7	30	Hypertensive pregnancy with severe IUGR	Yes	6–30
8	26	Spontaneous labor	No	7–26
9	39	Noonan's syndrome	Yes	5–18
10	23	Unexplained FDIU (recurrent)	Yes	6–18
11	24	One of twins, spontaneous labor	No	5–18
12	25	Spontaneous labor	Yes	7–18
13	28	PROM & subsequent labor	Yes	6–18
14	25	PROM & subsequent labor	Yes	6–18
15	28	Unexplained stillbirth	No	5–18
16	24	Abruptio placentae (1 of twins)	No	6–18
17 and 18	24	PROM & subsequent labor (twins)	No	5–24
19	24	PROM & subsequent labor (twins) (1 of twins)	No	6–18

[1]PROM = premature rupture of membranes; IUGR = intrauterine growth retardation; IUGR = intrauterine growth retardation; NND = neonatal death; PROM = premature rupture of membranes; FDIU = fetal death in utero.

subsequently thrived. His age is now 2 years.

The case listed as a combined renal and genital anomaly was in a female with normal XX karyotype who has been shown to have a single pelvic kidney and renal failure. At cystoscopy, vaginal agenesis was noted. She required a ureterostomy and is now thriving. Apart from the case with Noonan's syndrome, no other cardiac defects were noted, and none of the 147 female infants exposed to MPA showed features of virilization.

DISCUSSION

This report makes no attempt to evaluate the efficacy of progestagen support therapy for the prevention of early pregnancy wastage. We have noted the controversial views and have drawn attention to the very high early fetal wastage that occurs in women conceiving after infertility treatments and deduced a need for definitive studies to evaluate the nature of the wastage and potential modes of treatment. The data reported in this study are unique in that they are able to examine a large population of patients exposed to relatively large doses of MPA and where the duration of exposure was extended throughout most of the organogenesis period.

In selecting MPA as a support progestagen for our patients, we were influenced by previous observations that the drug did not cause significant congenital abnormalities, and in the case of virilization of one female infant amongst 170 newborn (Burstein and Wasserman, '64), only mild clitoral hypertrophy was noted. Derivatives of the 19-norethisterone group have been used in the past and have been clearly shown to have appreciable androgenic effects on the developing female fetus (Wilkins, '60). We have also seen female virilization associated with the use of both hydroxyprogesterone hexanoate and hydroxyprogesterone caproate. The orally active agent of MPA was chosen rather than the depot form since the latter

TABLE 5. Abnormalities identified in infants arising from infertility treatments

	Abnormality	Outcome	Cases
Matched group (not exposed to MPA)			
Major			
Male	Hydrocephaly	Surgical repair	1
Male	Hypospadias	Surgical repair	1
Male	Bilateral undescended testis	May require surgery	1
Female	Cleft palate	Surgical repair	2
Female	Diaphragmatic hernia	Surgical repair	1
Male	Spina bifida	Terminated at 18 wk	1
Male	Phocomelia in two limbs	Thriving	1
Male	Congenital hyperthyroidism	Thriving	1
Female	XXX Syndrome	Terminated at 18 wk	1
Unknown	History of myotonia dystrophia	Terminated at 8 wk	1
Male	Talipes equinovarus	Treated	1
Male	Tracheo-esophageal fistula	Surgical repair	1
Male	Pyloric stenosis	Surgical repair	1
Minor			
Male	Metatarsus varus	Thriving	1
Total abnormalities			15

	Abnormality	Outcome	MPA exposure (weeks)	Cases
Groups exposed to MPA				
Major				
Female	Combined renal and genital anomaly	Thriving with nephrostomy	6–18	1
Male	Body-wall defect with limb reduction anomaly (thoracogastroschisis)	Stillborn	7–8	1
Male	Noonan's syndrome	Neonatal death	5–18	1
Male	Klinefelter's syndrome	Thriving	5–18	1
Male	Bilateral inguinal hernia	Surgical repair	6–18	1
Female	Hemivertebrae & ribcage anomalies	Thriving	6–18	1
Male	Deformity of right pinna	Surgical repair planned	6–18	1
Male	Tracheo-esophageal fistula	Surgical repair	5–18	1
Male	Hydrocephaly	Surgical repair	5–18	1
Male	Goldenhar syndrome	Thriving	5–18	1
Female	Incontinentia-pigmenti (autosomal-dominant trait)	Thriving	5–18	1
Minor				
Male	Glandular hypospadias	Healthy	6–18	
			5,6–18	2
Male	Bilateral hydrocele	Resolved spontaneously	5,6–18	2
Total abnormalities				15

has been noted occasionally by us to maintain the basal temperature and inhibit ovulation for several months after spontaneous abortion. Further data from the PIVET Medical Centre (Yovich et al., '85d) have shown that MPA is well absorbed orally, and stable plasma concentrations around 26.8 ± 5.0 nmol/l are established during the course of therapy when given according to the schedules described. That study also examined the profile of steroid metabolites in the maternal urine during the first trimester of pregnancy and showed no abnormal peaks on gas-liquid chromatography and mass spectometry in a controlled series.

In Western Australia, a Congenital Malformations Register was established in 1980 (Bower and Stanley, '86), noting the rate of significant malformations to range between 3.2% and 4.5% of infants delivered between the years 1980 and 1985 inclusive, without including the very minor abnormalities such as umbilical hernia, hydrocele of the testes, and possibly some minor cases of hypospadias. In analyzing abnormalities associated with MPA therapy, we found that 11/318 (3.5%) demonstrated major abnormalities, a further two had spontaneously resolving hydroceles, and another two (0.6%) had mild hypospadias affecting the glans penis and not requiring surgery. The association has been recorded previously (Kupperman, '61), and the glans region is thought to be an area of predilection for MPA (Aarskog, '79). However, the observation of hypospadias in this series is not

significant when compared against a matched series. Figures obtainable from the Western Australian Congenital Malformations Register indicate a local incidence of hypospadias of around 1/200 male infants. This has been consistent over the years 1980 (prior to this study) to 1983. This is a higher incidence than generally quoted (Wilkinson, '73). The reasons are unknown but may be due in part to the determined efforts of data collection for the Register, which utilizes a multiple reporting system. There are a number of reports showing that the incidence of hypospadias has risen for unknown reasons in recent years—from 0.15% in 1964 to 0.36% in 1983 (Lancet Editorial, '85). Against this background, our observations rule out the possibility of MPA causing hypospadias. The hydrocele observations are also insignificant as their natural incidence is >2%.

It therefore appears unlikely that either major or minor abnormalities were due to MPA usage. We did consider the possibility of MPA inhibiting the abortion of abnormal fetuses, but this is not suggested by the data. The stillborn infant had defective bodywall development, probably because of early rupture of the amniotic membrane, with subsequent amniotic band formation. This is quite different from the congenital limb reduction deformities reported in another Australian series (Kricker et al., '86), and no other examples were noted in our series. Furthermore, in the Kricker study there were several methodological errors. They included patients in the exposed group in the first 3 weeks of pregnancy (from the last menstrual period), a time when limb reduction defects are not produced by environmental teratogens, and they had an inordinately low breakthrough pregnancy rate, indicating marked underascertainment in their controls. Furthermore, the report by Katz et al. ('85) is also consistent with our findings as well as with other reports dealing with exposure to a spectrum of progestins. The other abnormal infant who died in the neonatal period resembled a described syndrome whose etiology is unknown. The third child, with a life-threatening abnormality, demonstrated anomalies of the renal and genital systems; it would not be reasonable to implicate MPA in the etiology as it was the only observed case in our series, and an association with progestagens is without precedent in published literature. Similarly, the child with Goldenhar syndrome is an isolated case with obscure etiology. Of course, we are mindful of the knowledge that diethylstilbestrol can be associated with defects that may not become obvious for 2 decades (Herbst et al., '72), and hence continuing observation and reporting of children exposed to MPA during fetal development is required. In this respect, although the animal studies have been reassuring, the potential for human data to vary from animal, including primate, studies should be considered. In addition one must consider that MPA may produce developmental delays rather than discrete anomalies. In this context we refer to the two reports by Hendrickx et al. ('85a,b) concerning Benedictin embryotoxicity causing delayed closure of the ventricular septum. This indicates that some forms of embryopathy might only be detected in preterm infants.

In this report we have included certain information regarding early pregnancy wastage, essentially to show the comparability of the MPA-treated groups to the untreated controls. Early pregnancy wastage was high in the three groups studied, and this is consistent with recent reports (Jansen, '82; Yovich and Matson, '88) that show a high proportion of wastage amongst women who conceive following infertility therapies. There is a bias toward increased wastage within the threatened abortion subgroup of MPA-treated women. Women who bleed in pregnancy and are therefore categorized as threatened abortion, have a significantly higher chance of losing their pregnancy before 20 weeks gestation because of ectopic pregnancies or blighted ovum pregnancies and miscarriages.

This report shows no risk of embryopathic damage when women are administered MPA in high doses during the period of organogenesis. Clearly, however, further control studies are indicated, and we wish to express caution, noting that no benefits have yet been shown of hormonal therapy during the first trimester of pregnancy and that any possible benefits can only apply to a relatively small subgroup of the reproductive female population. Any agent utilized during the period of organogenesis is potentially hazardous, and for this reason the use of MPA should continue to be analyzed within structured research protocols, with careful monitoring of pregnancy outcome,

congenital abnormalities, and long-term developmental progress, including studies designed to detect remote disorders.

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