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Original Article

MPA given orally during the first trimester for threatened miscarriage carries no specific risk for foetal abnormalities albeit the rate is higher than non-threatened pregnancies

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ABSTRACT

This observational study examines the outcomes of pregnancies arising in women referred for infertility, where those who experienced threatened miscarriage were treated with medroxyprogesterone acetate (MPA) tablets. The 14-year study period covers comprehensive real-time data entries into the validated electronic database including details of the infertility management, pregnancy outcomes and any foetal anomalies among the infants, each being tracked and recorded. Of 4057 clinical pregnancies, 1343 received MPA for threatened miscarriage; 934 (69.6 %) of which continued to livebirths. These were compared with the remaining 2714 clinical pregnancies without threatened miscarriage or MPA and which resulted in 2075 (76.5 %) livebirths. There were 134 developmental abnormalities recorded among the 3009 livebirths of which 78 (2.6 %) were categorised appropriate for the Western Australian Developmental Abnormalities Register; WARDA. These comprised 55 in the MPA group, 36 of which were categorised as serious (being 2.7 % of clinical pregnancies and 3.9 % of births). In the group without MPA, there were 79 abnormalities, of which 42 were categorised as serious (being 1.7 % of clinical pregnancies and 2.2 % of births). Specifically, there were no cases of androgenisation noted among the female infants. The abnormality rates were low overall and well within the annual WARDA ranges. We cautiously suggest that oral MPA can be considered for studies throughout pregnancy including the early first trimester to assess a potential role in reducing miscarriage, as well as advanced pregnancies to evaluate a potential role in reducing stillbirths and preterm delivery.

1. Introduction

Threatened miscarriage is an adverse pregnancy event that can lead to serious complications for the developing foetus and increases the risk of pregnancy loss (PL). Vaginal bleeding occurs in about 25 % of pregnancies and approximately 50 % of these will go on to spontaneously abort [1–4]. For those pregnancies which continue, there is a higher rate of obstetric complications and an increased risk of congenital foetal abnormalities [4–7]. Furthermore, threatened miscarriage in the setting of infertility management, particularly that by in-vitro fertilization (IVF), is associated with a further 20 % increase in the risk of PL [8]. The reasons for this elevated risk may be an extension of the infertility disorder or relate to higher psychological stress levels experienced by women with infertility or history of miscarriages [9,10]. Such stress levels can be categorised as underlying or directly related to the intense investment of time and finances in managing the infertility issue by assisted reproduction [11,12].

For those experiencing threatened miscarriage, management is expectant but may include bed rest, avoiding intercourse and possibly progestogen or progesterone administration [13], although this has been controversial for two reasons. Firstly, studies from the 1960s failed to show any reduction in PL's from progestogen therapy [14]; and secondly, some progestogens had been associated with foetal abnormalities [15–17]. For these reasons, authoritative bodies such as the Royal Australian and New Zealand College of Obstetricians and Gynaecologists Consensus wrote that MPA is not recommended for pregnant women or those who have undiagnosed abnormal vaginal bleeding [18]. The recent Monthly Index of Medical Specialties (MIMS;

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published in the UK since 1959 and Australia since 1963) issue placed MPA in category D, as advised by the Therapeutic Goods Administration, which means it is classified as contraindicated in women who are, or may become, pregnant [19,20].

Notwithstanding the aforementioned concerns about foetal abnormalities as well as limitations of efficacy, clinicians have continued to explore the use of progestogens, particularly in the modern era of infertility management by IVF, where a wide variety of hormonal agents have been applied to control the ovulatory process as well as cover luteal defects and early pregnancy weaknesses. With respect to progestins, an improved understanding of the categories [21] including the relevance of the two progesterone receptors (isoforms A and B), has led to exploring specific progestogens for wider use; both for improving implantation rates and for improving pregnancy outcomes [22].

At PIVET Medical Centre, we have used MPA since 1980 for those patients who were managed for infertility and who presented with threatened miscarriage in their ensuing pregnancies [23–29]. Apart from clinical outcomes we reported on metabolic studies during pregnancies treated with MPA [30]. We also reported that these studies during the 1980s showed no apparent specific teratogenic effects from MPA [31]. This current study reports on the questions of maternal safety and foetal teratogenicity in a carefully collated further series covering 14 years, where each pregnancy outcome is well documented.

2. Materials and methods

2.1. Study cohort and patient group selection

This retrospective study examined all clinical pregnancies arising at PIVET Medical Centre from 1st January 2004 to 11th September 2017 (n = 4057) with delivered outcomes recorded to 20th June 2018. The centre is a tertiary referral site for infertility and provides comprehensive services across the broad range of treatments including cycle tracking with timed intercourse through to in-vitro fertilization (IVF) methods [32]. Over the study period an increasing proportion of pregnancies were achieved by frozen embryo transfer (FET) as the adoption of a single embryo transfer policy for more than 90 % of IVF treatments has translated to a higher number of blastocysts being cryopreserved. The FET cycles have been conducted under natural cycle tracking, using low dose ovarian stimulation or, increasingly, under a hormone replacement schedule. In all cases, the protocol requires monitoring to optimise mid-luteal progesterone levels [33]. MPA has been used at the centre since its inception in 1980, but the start date for this study was selected as the time when clinical treatment data recording was comprehensive enabling all infant abnormalities to be traced and recorded within the validated electronic database. All cycles and patients were included for analysis and categorised on the basis of MPA (Provera tablets) administration. Attending clinicians prescribed MPA if the clinically pregnant patient presented with abnormal vaginal bleeding in the 5th–8th week of pregnancy and received MPA until at least the 14th week of gestation (N = 1343 cycles). Routine trans-vesical ultrasound was applied for pregnancy evaluation but was considered unreliable for diagnosing viable pregnancy before “day-49” meaning 7-week gestation. Therefore, prior to this date or if gestational dating was uncertain, MPA was offered on all cases of vaginal bleeding; after this date, only those women with a viable foetus were treated with MPA. These cycles were identified as (+)MPA. Comparator cycles included women who were clinically pregnant but not presenting with vaginal bleeding [i.e. not receiving MPA, defined as (−)MPA], and were examined for background miscarriage and infant abnormality rates (N = 2714 cycles). The vast majority of patients who were offered MPA accepted its use to prevent further abnormal bleeding and provided appropriately informed consent.

2.2. Clinical management

Since the patients were attending a fertility clinic, they were sub-categorised on the basis of the treatment cycle type they were undergoing. This included women undergoing an assessment cycle which resulted in a spontaneous clinical pregnancy (N = 761), patients undergoing intra-uterine insemination or ovulation induction cycles (IUI-OI, N = 179), those undergoing an IVF stimulation cycle and fresh embryo transfer (N = 1495) and finally women undergoing frozen embryo transfer (FET) cycles (N = 1622).

2.3. Definition of live birth, pregnancy loss and foetal abnormality

Infant outcome including the presence of foetal abnormalities, was confirmed by regular follow up with the attending obstetricians after the estimated date of delivery (EDD). Follow-ups were also made directly with the patients after the EDD. In fact, all the cases reported in this study had a post-delivery “chat” with a dedicated midwifery nurse who covered this entire period. She formed a close relationship with each of the women who delivered and received further information about the ensuing progress of the children as well as answering the question of any untoward maternal effects from the MPA. Live birth (LB) deliveries were categorised as very early preterm, preterm and full term if the number of gestation days was 140–195, 196–258 and ≥259 days, respectively. Pregnancy loss (PL) was categorised as either 1st trimester PL, mid-trimester PL, preterm stillbirth or full-term stillbirth if the foetus was lost/delivered during gestation days 49–90, 91–139, 140–258 and ≥259 days, respectively. Each foetal abnormality was categorised according to the International Classification of Disease (ICD) code, and then sub-categorised into the related anatomical system including neural, eye defects, cardiovascular, gastrointestinal, urogenital, musculo-skeletal, skin, chromosomal and any other.

2.4. Statistical analyses

None of the continuous data were normally distribution as determined using the Shapiro–Wilk test. Therefore, the non-parametric Kruskal–Wallis test was used to compare medians of continuous data. Categorical variables were compared using Chi-square of ratios. Univariate and stepwise multi-variable binary logistic regression models were used to determine the influence of confounding variables in predicting risk of pregnancy loss (PL) and development of serious abnormalities. These included MPA use, the cycle type, female age, serum anti-Mullerian hormone (AMH), body mass index (BMI), previous PL events, previous assisted reproductive technology (ART) interventions, pregnancy with multiples, gestational days of the foetus, gender of the infant and birth weight. The effect of each variable was expressed as an Odds Ratio (OR), with corresponding 95 % Confidence Interval (CI). Finally, multi-variable binary logistic regression models were developed to adjust data according to significant univariate factors, and to determine the association between MPA use and cycle type with risk of PL and serious abnormalities.

2.5. Ethical considerations

Ethical approvals were initially provided by the Committee for Human Research at UWA, and later, in 1986, transferred to Cambridge Hospital Ethics Committee following the establishment of the private PIVET Medical Centre facility. Protocols for consent to use Provera at PIVET are embraced under File #18 *Information & consent for the use of drugs and hormones for luteal support and during pregnancy*. All protocols are endorsed under licence from the Reproductive Technology Council (RTC) of Western Australia (Practice Licence current to April 2021) as well as the Reproductive Technology Accreditation Committee (RTAC) under the auspices of the Fertility Society of Australia (accredited to April 2020). The reporting of this retrospective data analysis was

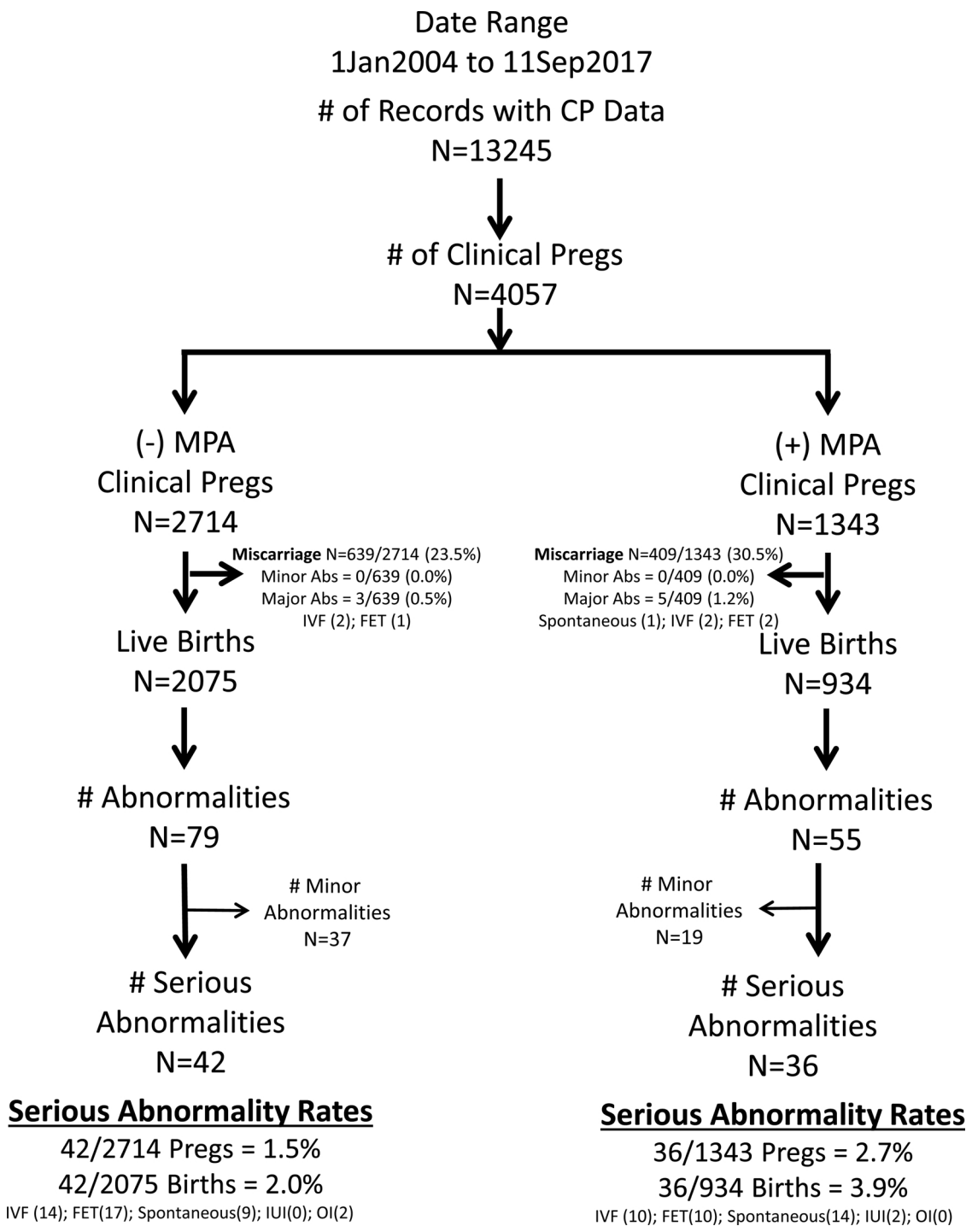

Fig. 1. Flow diagram depicting the method of analysis. All clinical pregnancies of the defined time range were documented for early vaginal bleeding and whether the women received MPA. The pregnancy loss (PL) and serious abnormality rate are compared for women receiving MPA; (+)MPA for early vaginal bleeding v those women who did not receive MPA; (−)MPA as they had no signs of threatened miscarriage. Abnormality rates were expressed as a fraction of clinical pregnancies and live births, with analyses showing rates lower than 4 %. IVF includes ICSI (~75 % across the study period).

provided by Curtin University Human Research Ethics Committee approval RD-25-10.

3. Results

Fig. 1 depicts an overview of all the pregnancies generated during the 13-year period and their allocation to MPA, along with the outcomes including miscarriages, various stages of pre-term births and all LBs and significant foetal abnormalities. Fig. 2 shows the distribution of foetal abnormalities across the various fertility treatments according to MPA use (those with threatened miscarriage) and compares those who had no miscarriage threat hence did not receive MPA.

3.1. Differences in demographic data between (−)MPA and (+)MPA groups

All accepting patients presenting with vaginal bleeding by gestational week-8 (i.e. threatened miscarriage) were administered MPA,

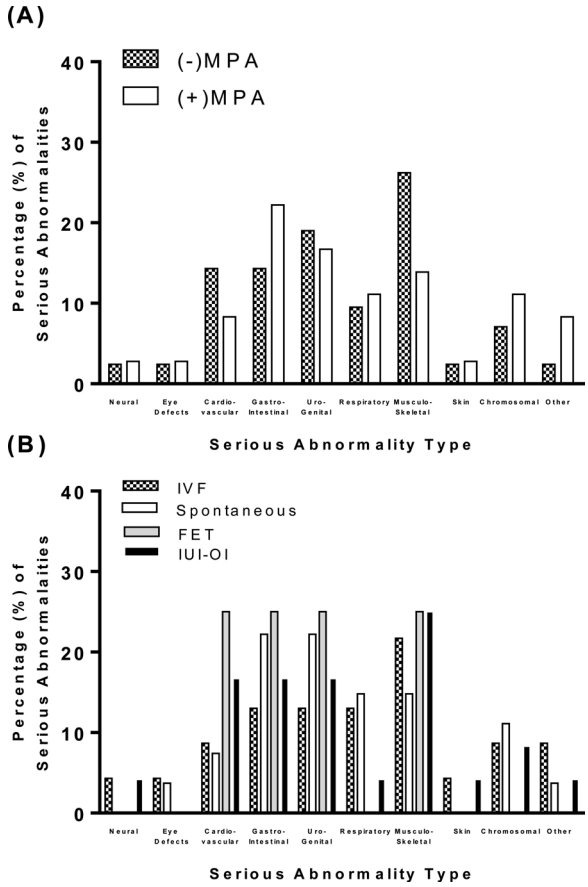

Fig. 2. Serious abnormality rates analysed according to body system and on MPA use (A) and treatment cycle type (B). Defects of the cardiovascular, gastro-intestinal, uro-genital, musculo-skeletal systems were most common, but occurred similarly across MPA use and treatment cycle type. No clear statistical pattern could be determined due to the low case numbers in each category.

and were significantly older than the comparator (−)MPA group by a median 1 year (Table 1). The (+)MPA patients also had a slightly higher BMI and the median gestation days for resulting live births was significantly lower in this group (Table 1). There was no significant difference in median ovarian reserve (AMH) or prior miscarriage history (i.e. RPL) between the MPA treatment groups (Table 1). However, 42.4 % of (−)MPA cycles corresponded to the very first ART event/intervention for this group, while only 32.5 % of the (+)MPA cycles corresponded to the first cycles for these patients. Therefore, the (+)MPA group had more previous ART events/interventions compared to the (−)MPA group (by 7.5 %). (+)MPA was also used in 17.3 % and 25.1 % of IUI-OI and IVF cycles respectively, while a much higher proportion of spontaneous and FET cycles resulted in the administration of (+)MPA (39.4 % and 39.3 %, respectively).

Maternal tolerance to MPA use was almost 100 %, with no more than 10 women declining to use it and only 3 cases ceasing use because of headaches; 2 of these resuming when vaginal bleeding recurred. Universally, women expressed satisfaction that the early pregnancy vaginal bleeding abated within 24 h and usually ceased completely over a few days.

3.2. Differences in clinical outcomes between (−)MPA and (+)MPA groups

The overall live birth rate per clinical pregnancy in the (−)MPA group was significantly higher than the (+)MPA group (76.5 % v 69.5 % respectively, $p < 0.001$), which was also reflected in a lower overall PL rate (23.5 % v 30.5 % respectively, $p < 0.001$) (Table 2). There were significantly fewer preterm deliveries (196–258 days) in the (−)MPA group v (+)MPA (10.8 % v 16.5 % respectively, $p < 0.001$), along with more full term deliveries (88.6 % v 82.3 % respectively, $p < 0.001$). There were no significant differences in very early preterm (140–195 days) birth rates at 0.5 % v 1.2 % respectively, $p = 0.065$ (Table 2). Similarly, 1st and mid-trimester pregnancy loss (PL) rates, along with preterm stillbirth rates, were not significantly different between the MPA groups (Table 2). Conversely, if pregnancies continued beyond 37 weeks (≥ 259 days) and resulted in a full term stillbirth, the rate observed for the (−)MPA group was significantly higher than the (+)MPA group at 5.5 % v 1.5 %, respectively, $p < 0.001$ (Table 2). Finally, although the abnormality rates were low in both groups, fewer abnormalities were observed in the (−)MPA group (Table 2), with the overall abnormality rate (minor and serious) per clinical pregnancy case at 3.0 % v 4.5 %, (−)MPA v (+)MPA respectively, $p < 0.05$. The serious abnormality rate per live birth case was also lower at 2.0 % v 3.9 %, (−)MPA v (+)MPA respectively, $p < 0.01$. The profile of these

Table 1
Demographic analysis according to MPA utilization/threatened miscarriage.

Demographic variables		(−)MPA	(+)MPA	Total	p-Value
CP cases, N		2714	1343	4057	–
Continuous variables					
Female age, median years (IQR)		34.0 (6.0)	35.0 (8.0)[A]	–	< 0.001
AMH, median pmol/L (IQR)		15.4 (22.1)	13.6 (23.4)	–	0.169
BMI, median kg/m^2 (IQR)		23.4 (5.8)	23.5 (7.1)[A]	–	0.011
Gestation days median (IQR)		270 (35.0)	264 (192)[A]	–	< 0.001
Categorical variables					
Cycle type, N (% of cycle type)	IVF	1120/1495 (74.9)	375/1495 (25.1)	1495	< 0.001
	Spontaneous	461/761 (60.6)	300/761 (39.4)	761	
	FET	985/1622 (60.7)	637/1622 (39.3)	1622	
	IUI-OI	148/179 (82.7)	31/179 (17.3)	179	
Previous PL, N (% of CP cases)	None	2345 (86.4)	1160 (86.4)	3505	0.999
	One	307 (11.3)	152 (11.3)	459	
	Two or more	62 (2.3)	31 (2.3)	93	
Previous IVF events, N (% of CP cases)	None	1151 (42.4)	436 (32.5)[B]	1587	< 0.001
	One	924 (34.0)	491 (36.6)	1415	
	Two or more	639 (23.5)	416 (31.0)	1055	

CP, clinical pregnancy; PL, pregnancy loss.
[A] Statistically different from (−)MPA group, median test.
[B] Statistically different from (−)MPA group, X^2 test.

Table 2
Analysis of clinical outcomes according to MPA utilization/threatened miscarriage.

Clinical outcomes		(−)MPA	(+)MPA	Total	p-Value
CP cases, N		2714	1343	4057	–
LB	Overall, N (% of CP cases)	2075/2714 (76.5)	934/1343 (69.5)[A]	3009/4057	< 0.001
	Very early PT, 140–195 days, N (% of LB cases)	11/2075 (0.5)	11/934 (1.2)	22	0.065
	PT, 196–258 days, N (% of LB cases)	224/2075 (10.8)	154/934 (16.5)[A]	378	< 0.001
	FT, ≥259 days, N (% of LB cases)	1840/2075 (88.7)	769/934 (82.3)[A]	2609	< 0.001
PL	Overall, N (% of CP cases)	639/2714 (23.5)	409/1343 (30.5)	1048/4057	< 0.001
	1st Trimester PL, 49–90 days, N (% of PL cases)	535/639 (83.7)	352/409 (86.1)	887	0.335
	2nd Trimester PL, 91–139 days, N (% of PL cases)	46/639 (7.2)	32/409 (7.8)	78	0.719
	PT stillbirth, 140–258 days, N (% of PL cases)	23/639 (3.6)	19/409 (4.6)	42	0.422
	FT stillbirth, ≥259 days, N (% of PL cases)	35/639 (5.5)	6/409 (1.5)[A]	41	< 0.001
Abnormalities	None, N (% of CP)	2632/2714 (97.0)	1283/1343 (95.5)	3915/4057 (95.7)	0.013
	All abnormalities, N (% of CP)	82/2714 (3.0)	60/1343 (4.5)	142/4047 (3.5)	0.013
	LB with *Minor* abnormality, N (% of LB)	37/2075 (1.8)	19/934 (2.0)	56/3009 (1.9)	0.662
	LB with *Serious* abnormality, N (% of LB)	42/2075 (2.0)	36/934 (3.9)	78/3009 (2.6)	0.006
	PL with abnormality, N (% of PL)	3/639 (0.5)	5/409 (1.2)	8/1048 (0.8)	0.274

CP, clinical pregnancy; LB, live birth; PL, pregnancy loss; PT, preterm; FT, full term.
[A] Statistically different from (−)MPA group, X^2 test.

serious abnormalities covered widely various anatomical structures, with the majority involving the gastro-intestinal and musculo-skeletal systems, but without displaying any recurrent findings related to MPA use (Supplemental Fig. 1A and B and Supplemental Table 1). In relation to the miscarried fetuses, there were 8 detectable abnormalities in total, all were considered serious and albeit in a small sample size, they were not significantly different between the MPA treatment groups; 3/639 v 5/409, (−)MPA v (+)MPA respectively, p = 0.274.

3.3. Logistic regression analysis of PL likelihood with MPA

The main predictors of increased PL likelihood were cycle type, female age, previous ART treatment events (as continuous variable only), and (+)MPA treatment (Table 3), as determined by applying univariate binary logistic regression. When the data was adjusted for female age in a multi-variable analysis, cycle type and previous ART attempts became insignificant for risk of PL (data not shown). However, after adjustment for both female age and cycle type, those in the (+)MPA group were 34 % more likely to experience PL (Table 3). For every year increase in female age, the chance of PL increased by 5 % regardless of MPA use and cycle type. However, while FET cycles were associated with an increased chance of PL in univariate analysis, this parameter was not significantly associated with increased PL following adjustment for female age and MPA use (Table 3). This indicated that MPA and female age were the primary independent predictors of increased PL risk in this dataset.

3.4. Logistic regression analysis of serious abnormality risk with MPA

The main univariate predictors of increased serious abnormality risk were cycle type, lower gestation days, lower baby weight and use of (+)MPA (Table 4). Those in the (+)MPA (threatened miscarriage) group were 1.9 times more likely to deliver an infant with a serious foetal abnormality, while those achieving a spontaneous pregnancy under infertility assessment were 2.0 times more likely to deliver an infant with a serious foetal abnormality when compared with the (−)MPA group who had no threat to miscarry (Table 4). As expected, shorter gestation and lower delivery birth weight was also associated with an increased risk of serious abnormalities. However, following adjustment for female age, cycle type, infant weight and infant gender in a multi-variable regression model, those children born to women in the (+)MPA group or achieving a spontaneous pregnancy, were at more risk of developing a serious foetal abnormality. Specifically, the (+)MPA group was 1.8 times more likely to experience serious foetal abnormalities, and in the same regression model, women with spontaneous pregnancies were 2.0 times more likely to deliver a child with a serious abnormality, regardless of MPA use or non-use (Table 4). As cycle type and (+)MPA were the only significant predictors of serious abnormality risk in this multi-variable model, we investigated whether there was a statistical interaction between these two factors. Using IVF treatment in cycle type and (−)MPA as reference groups, the analysis revealed no significant interaction was present between cycle type and MPA use (p = 0.18) (Table 5). This indicated that both factors were

Table 3
Univariate and multi-variable logistic regression analysis of the chance for pregnancy loss (PL).

		Likelihood of pregnancy loss (PL)			
		Univariate (unadjusted)	p-Value	Multi-variable regression (adjusted)[A]	p-Value
MPA use	(−)MPA	1.00	–	1.00	–
	(+)MPA	1.42 (1.23–1.65)	< 0.001	1.34 (1.16–1.56)	< 0.001
Cycle type	IVF	1.00	–	1.00	–
	Spontaneous	1.19 (0.97–1.45)	0.092	1.15 (0.94–1.40)	0.184
	FET	1.21 (1.03–1.42)	0.019	1.12 (0.95–1.32)	0.180
	IUI-OI	0.77 (0.52–1.14)	0.191	0.84 (0.57–1.23)	0.366
Female age		1.05 (1.03–1.06)	< 0.001	1.05 (1.03–1.06)	< 0.001
Serum AMH		1.00 (0.99–1.00)	0.238	–	–
BMI		1.01 (1.00–103)	0.074	–	–
Previous PL (continuous)		1.10 (0.94–1.28)	0.239	–	–
Previous ART events (continuous)		1.05 (1.00–1.10)	0.042	–	–

[A] MPA data adjusted for cycle type and female age.

Table 4
Univariate and multi-variable logistic regression analysis of the chance for serious abnormalities across a range of variables.

Variable		Likelihood of serious abnormality			
		Univariate (unadjusted)	p-Value	Multi-variable regression (adjusted)[A]	p-Value
MPA use	(−)MPA	1.00	–	1.00	–
	(+)MPA	1.94 (1.24–3.05)	0.004	1.75 (1.10–2.80)	0.019
Cycle type	IVF	1.00	–	1.00	–
	Spontaneous	2.01 (1.12–3.59)	0.019	2.04 (1.12–3.70)	0.019
	FET	1.09 (0.63–1.90)	0.757	1.05 (0.59–1.86)	0.865
	IUI-OI	1.32 (0.45–3.87)	0.607	1.51 (0.51–4.45)	0.454
Female age		1.01 (0.96–1.06)	0.699	1.01 (0.96–1.06)	0.739
Serum AMH		0.99 (0.98–1.01)	0.213	–	–
BMI		1.01 (0.97–1.07)	0.583	–	–
Previous PL (continuous)		0.611 (0.30–1.23)	0.168	–	–
Previous ART events (continuous)		0.89 (0.74–1.08)	0.240	–	–
Gestation days (continuous)		0.99 (0.976–0.996)	0.009	–	–
Infant weight		0.999 (0.999–1.000)	0.002	1.00 (0.999–1.000)	0.072
Infant gender		1.07 (0.68–1.67)	0.777	0.998 (0.981–1.014)	0.775

[A] MPA data adjusted for cycle type, female age, infant weight and infant gender.

Table 5
Interaction analysis of serious abnormality risk and treatment cycle type.

	Likelihood of serious abnormality	
	Interaction odds ratio	p-Value
MPA use*cycle type[A]		
(+)MPA*IVF	1.00	0.128
(+)MPA*spontaneous	1.05 (0.32–3.43)	0.941
(+)MPA*FET	0.36 (0.12–1.13)	0.080
(+)MPA*IUI-OI	2.46 (0.28–21.8)	0.418

[A] IVF cycle type and (−)MPA used as reference group.

completely independent from each other and were independent predictors for increased serious foetal abnormality risk.

4. Discussion

4.1. Interpretation of the data

The main purpose of presenting this data was to show that foetal abnormalities are not increased above the backgound community level by the use of MPA in the setting of pregnancies arising from infertility treatments. With a rate under 5 %, we believe this aim is fulfilled. The question of untoward maternal effects was also found to be almost zero hence we have no hesitation in re-assuring our patients from these data. However, the study has limitations in answering other questions about the utility of MPA to improve pregnancy outcomes. Bearing in mind that MPA was given to women who were already threatening pregnancy loss, this report does not properly study the likelihood of MPA reducing that chance of loss. Such would require allocation of women with threatened miscarriage into an MPA-treatment v non-treatment group, preferably randomised. In this study, the threatened miscarriage group; (+)MPA, did not show any reduction in PL rate in women when compared with the non-threatened miscarriage group; (−)MPA. In fact, its use was actually associated with a 34 % increased chance of PL when analysed using logistic regression and adjusted for female age and cycle type. However, when the late PL rate of > 20 weeks (≥140 days) was examined between the two groups, the rate was lower with (+)MPA, albeit not significantly different from (−)MPA (6.1 % v 9.1 %, respectively). However, those with (+)MPA did show a significantly lower full term stillbirth rate (≥ 259 days) in comparison to the (−)MPA group. Taken together, this indicated that if those receiving (+)MPA for early abnormal vaginal bleeding in the current study retained the pregnancy through to 37 weeks, there was a significantly lower risk of delivering a stillborn infant in comparison to those not receiving MPA. These findings echo our previous report 30 years ago [30], where the later PL rate (> 20 weeks) was not significantly different between (−)MPA and (+)MPA (3.7 % and 5.9 %, respectively). However, both studies indicated that those with threatened miscarriage were at a much higher risk of early PL. Both studies were limited by the characteristics of the comparator group i.e. (−)MPA, who had no threatened miscarriage and comprised a significantly younger population, in comparison to those facing threatened miscarriage and consequently receiving (+)MPA. Therefore, the PL rate in both reports are likely underestimated in the (−)MPA comparator group as those who may have miscarried have been selected out for MPA treatment. Whilst this is a significant weakness in both investigations, the clinical trends are similar.

4.2. Historical studies on MPA

MPA is a substituted progesterone, both hormones being pregnane derivatives, but MPA is specifically categorised as a 17-hydroxyprogesterone derivative [21]. It has potent progestational activity and was shown to be 20–50 times more potent e.g. enhancing implantation in castrated rabbits, than natural progesterone [34,35]. Very few studies have focused on the effect of MPA to reduce PL, but the first animal studies to show a potential benefit was in laboratory rabbits and in rats following parenteral administration [36]. Later in 1965, a placebo controlled double-blind study of women with threatened abortion failed to show that oral administration of MPA reduced overall PL risk, although there was a slight but insignificant reduction in PL when MPA was administered within 24 h of onset of vaginal bleeding [37]. A recent meta-analysis of ten RCTs investigating 1586 pregnant females with a history of RPL, found that progestogen support in the first trimester led to a reduction in relative risk (RR) for miscarriage (RR 0.72, 95 % CI 0.53–0.97) and increased the likelihood of LB (RR 1.07, 95 % CI 1.02–1.15) [38]. An updated Cochrane systematic review utilised similar studies with a total of 2556 RPL patients, demonstrating comparable reductions in PL risk (RR 0.69, 95 % CI 0.51–0.92) and increased likelihood of LB (RR 1.11, 95 % CI 1.00–1.24) in patients receiving progestogens [39]. Importantly, both studies included only one RCT using MPA, and this was in a small (N = 16), older trial from 1964 [40] which showed that MPA reduced the PL rate in comparison to placebo (25 % v 40 %, respectively), but the risk rate was not significant (RR 0.63, 95 % CI 0.15–2.59).

4.3. Proposed hypothesis of MPA action – enhancing placentation

In our current study, MPA was administered in order to prevent further bleeding, to allay anxiety and maintain pregnancy until a definitive ultrasound scan by 8-weeks could determine viability of the pregnancy. MPA was indeed spectacularly successful at stopping the vaginal bleeding (data not shown) but the (+)MPA group displayed a

lower LB rate, lower full term delivery and a higher preterm delivery rate which suggested that the (+)MPA patients were possibly less fertile and less capable of maintain their pregnancies to term. We would propose that this threatened miscarriage group had what might be termed "defective placentation", a phenomenon which displays itself throughout the pregnancy and which might benefit from MPA progestogen support. For example, although there was no difference in previous miscarriage/PL history between the treatment groups, a higher proportion of the (+)MPA patients had previous ART interventions, which indicates that they required greater assistance in conceiving. Specifically, for every additional ART treatment cycle, the probability of PL increased by 5 %, but this became insignificant after adjusting for female age. Similarly, when specific ART intervention treatment types, rather than number of events, was investigated, the data initially indicated that FET cycles were associated with increased PL (by 21 %), but this disappeared when adjusting for age. Overall, these data suggested that female age and MPA (threatened miscarriage) were the main predictors for PL risk, with the latter representing a group at significant risk of PL due to vaginal bleeding and poor prognosis. However, specific ART cycle types and number of treatment events were not predictors of PL in patients undergoing infertility treatment.

4.4. The relevance of threatened miscarriage among risk factors for foetal abnormality

In the current study, the (+)MPA group had a higher risk of producing an infant with serious abnormalities, even though the rate of 3.9 % was lower than the overall abnormality rate of 5.4 % for all natural and assisted births recorded in the Western Australian Register of Developmental Anomalies (WARDA) 1980–2014 [41]. Importantly, those who had a spontaneous pregnancy in the study group were two times more likely to deliver an infant with serious abnormality regardless of MPA administration. It is possible that these women had an underlying and/or undefined infertility problem that led to an increased risk of abnormalities over and above the use of MPA, which may at least in part, be related to the ploidy and/or quality of the gametes. Furthermore, since these spontaneous pregnancies occurred in an infertile population undergoing cycle tracking, the women did not receive the type of automatic luteal management in early implantation that would be used by a clinic in a fresh IVF or FET cycle on the basis of emerging hormone profile. This could include a parameter such as progesterone deficiency, an entity being increasingly recognised leading to a significant difference in cycle and pregnancy management [42]. It must be noted that there was a slightly higher proportion of these spontaneous pregnancies in the (+)MPA group. The findings show similar abnormality rate to that of our previous publication [30]. In that study, 366 (+)MPA cases were examined for incidence of serious congenital malformation, and compared to a control group of 428 cases matched for age, treatment method, infertility type and duration. There were 15 cases in each group with abnormalities, giving an abnormality rate of 4.1 % in the (+)MPA group and 3.5 % in the (−)MPA group. Four of the (+)MPA abnormal cases were minor, including 2 cases with hydrocoeles that regressed spontaneously and 2 cases with hypospadias that did not require surgery. These abnormality rates were not significantly different between the treatment groups and were no greater than the foetal abnormality rate of 4.3 % of delivered infants reported at the time in Western Australia by WARDA [43]. They were also spread across various organs and systems like the present study. Furthermore, the investigation reported in 1988 [30] included a control group that did not have vaginal bleeding and consequently, there was a bias towards lower wastage and possibly fewer abnormalities in the (−) MPA group. Again, this a recognised weakness of both studies.

4.5. The question of teratogenicity from progestagens

Other research has been conducted on the potential teratogenic and particularly the androgenic/virilisation effects of progestogens administered during pregnancy. The first report of an association between oral synthetic progestogen use and non-adrenal masculinisation of the female external genitalia in humans was in 1958 where 17-alpha-ethinyl-testosterone was used [15]. Such 19-nortestosterone derivatives, particularly those with a structure related to 17-alpha-methyl-testosterone can cause masculinisation, while pregnane derivatives including MPA do not [44]. However, whist one animal study in 1961 indicated that MPA increased masculinisation of the female rat [45], this was not observed in other animal studies examining rat and rabbit [35,36]. The first investigation of the effect of oral MPA on the human foetus was reported in 1964 [46]. In an uncontrolled study with 239 pregnant women treated with MPA (Provera) due to bleeding (n = 100), as a prophylaxis because of previous loss (n = 54) and due to abdominal cramps (n = 18), Burstein and Wasserman showed that only one case was identified with a congenital abnormality (congenital heart disease). One other female infant was diagnosed with transient masculinisation and clitoral hypertrophy, which subsided after 6 months. In addition, the double-blind RCT reported by Moller and Fuchs in 1965 [37] included 260 patients with threatened abortion and detected only one case of an infant with vaginal hypertrophy and a sagittal septum in the oral MPA group, but no other abnormalities were detected in 139 delivered infants. Further studies in 1977 demonstrated that in a small group of MPA-exposed female (n = 15) and male infants (n = 13) from week 2–34, MPA exposure during gestation was not associated with increased genital abnormalities in comparison to controls matched for sex, ethnicity, birth date, socio-economic status and vaginal bleeding in pregnancy [47,48]. These reports indicate that MPA had no significant effect on sexually dimorphic behaviour in males, but a subtle feminisation effect in females, which is somewhat contrary to the purported biological androgenisation effects of MPA.

4.6. Depo-MPA studies

The controversy surrounding MPA use is mainly related to the administration of the injectable DMPA formulation in contraception, which is different (dosage and various excipients) from the oral formulation used in the present study. This controversy is linked to a plethora of debatable user side effects such as increased weight-gain and risk for hypertension [49], mood changes and depression [50,51], decreases in bone mineral density [52] and more recently potential increased susceptibility to HIV infection [53,54]. However, DMPA is very effective in preventing conception with no pregnancies reported in 16,023 cycles using a new subcutaneous formulation [55]. In a larger study, less than 1 % of 949,182 DMPA patients reported pregnancy over a 5-year period [56]. These contraceptive failures occur before or shortly after the injection of DMPA and allow the study of potential associations between DMPA use and serious foetal abnormalities in those pregnancies which continued. In 402 women who were diagnosed with pregnancy after administration of DMPA, no abnormalities were recorded [55]. However, only 100 women continued with the pregnancy, while 111 had an induced abortion, 11 had a spontaneous abortion, 4 had an ectopic pregnancy, 4 were undecided and 172 had an unspecified outcome [56]. Other older studies have also indicated no significant increase in congenital anomalies with DMPA used for contraception [57–59]. While the debate surrounding the safety and efficacy of DMPA will continue, it is clear that it is an effective contraceptive, and the balance between the potential side effects for the woman and contraceptive benefits need to be considered on an individual basis. However, no studies have specifically shown a clear causal relationship between DMPA and congenital malformations, and certainly not between oral MPA use and foetal abnormalities.

4.7. Other progestagens

Recent developments have shown the potential of other

progestogens such as dydrogesterone (DYD) to support early pregnancy by modulating immune cell activity [60]. Various progesterone trials including LOTUS I and LOTUS II have shown positive outcomes in LB rates. In the LOTUS I trial, DYD was not associated with an increase in congenital abnormalities in comparison to micronized vaginal progesterone (6.6 % v 7.6 %, respectively) [61]. However, there is still debate regarding precisely at what point during the cycle agents such as DYD should be applied. In addition, there are other investigators who have used MPA 10 mg tablets/day during hMG ovarian stimulation from day 2 to day 5 and have not observed significant increases in abnormality rates [62]. In 1931 births using this protocol, there were 22 incidences of serious foetal abnormalities (1.1 %), which were mainly related to the circulatory system (36 %), indicating safety of the treatment.

4.8. Concluding remarks

In conclusion, this report indicates that infertile women who use MPA for threatened miscarriage will experience a higher rate of foetal abnormalities than those infertile women who do not experience first trimester vaginal bleeding and therefore do not use MPA. However, the risk levels for serious foetal abnormality in both groups is low, being no greater than 3.9 % of livebirths; a level which is lower than rates reported from the general community. The difference in abnormality rates among the infertile women was not influenced by the mode of conception when comparing IVF, FET and IUI generated pregnancies. However, infants from infertile women who are referred to IVF clinics and experience spontaneous pregnancy may be at a higher risk of developing foetal malformations. A significant reduction in late-stage stillbirths was noted in the MPA group, which may possibly indicate enhanced placentation. However, due to the increase in foetal abnormality risk in combination with the reduced stillborn rates, these data led to the potential question of whether MPA support can cause the retention of an abnormal embryo or foetus that would otherwise abort. Further studies are required to examine this question. In the meantime, we believe this data on MPA opens the window to exploring its use throughout pregnancy, particularly into late pregnancy as a potential support adjuvant to reduce the currently intransigent problem of preterm birth [42]. It appears to be quite safe for both women and their babies, whilst having a physiological action more potent than progesterone, which itself has recently been shown to be ineffective in reducing PL for threatened miscarriage; PRISM trial [63]. An earlier study by the same group showed progesterone to be also ineffective for treating recurrent miscarriage; PROMISE trial [64]. Our report, whilst not structured to prove a benefit for MPA in reducing PL for threatened miscarriage, provides reassurance that foetal abnormalities are not elevated above the non-infertile community, nor is there any recurring anomaly such as androgenisation of female infants. From our perspective this opens the door to a range of studies with MPA for luteal support, early pregnancy support and, in later pregnancy, with a view to reducing the risk of stillbirths and pre-term deliveries in high-risk scenarios.

Author contributions

The study was an initiative of JLY and KNK with each supervising equally. KNK, UM and PMH undertook data extraction. Data analysis was performed by KNK, UM and SSD. KNK and UM drafted the first version of the manuscript. All authors contributed substantially to manuscript revision and ideas presented in the Discussion.

Compliance with ethical standards

Our clinic is accredited with the national self-regulatory body Reproductive Technology Accreditation Committee; as well as the Reproductive Technology Council of Western Australia acting under specific legislation. Specific ethics approval was not required for this study as all procedures and blood tests were embraced by routine approved clinical protocols. However, retrospective analysis and reporting of the data was approved under Curtin University Ethics Committee approval no. RD_25-10.

Declaration of Competing Interest

The project was funded internally under an existing long-term collaboration between PIVET Medical Centre and Curtin University, which supports a Fellowship position for KNK. JLY is Medical Director of PIVET and adjunct Clinical Professor at Curtin University. The corresponding author JLY can confirm that none of the authors have any conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.repbio.2020.03.008.

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