Randomized Trial of Artesunate and Mefloquine in Comparison with Quinine Sulfate to Treat *P. falciparum* Malaria Pregnant Women

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Abstract

To compare the effectiveness and safety of quinine sulfate and artesunate with mefloquine for treating second trimester pregnancy in women who suffered from *Plasmodium falciparum* malaria. The prospective study was done in Srisangwal Hospital, Mae Hong Son, Thailand. Sixty, second to third trimester pregnant patients with *P. falciparum* infection, were recruited at random. They received either quinine sulfate 10 mg/kg/day for at least 7 days, 29 women (group I), or oral artesunate 2 mg/kg as the first dose, 1 mg/kg every 12 hours orally for at least 5 days together with split doses of mefloquine, 15 mg/kg and 6 hours later 10 mg/kg orally 1 day after artesunate was stopped, 28 women (group II). Three cases (5%) were lost to follow-up before delivery, one case in group I and two cases in group II. After treatment, the mean hematocrit of group I was significantly less than group II ($p = 0.000$). The PCT (parasite clearance time) and FCT (fever clearance time) of group II were significantly shorter than group I ($p = 0.000$). None of the patients in both groups had recrudescences within 28 days. Group I had more adverse effects than group II. No adverse neurological effects in pregnancy were found in both groups. The calcification of placenta and IUGR (Intrauterine growth retard) were not different between the two groups ($p = 0.964$, 0.363 respectively). The PCT was not different between the calcified placenta group and normal placenta group ($p = 0.058$), but the TTPP (Total time of parasite presentation) was ($p = 0.000$). TTPP related to low birth weight and low apgar score at 1 minute might be the cause ($p = 0.000$, 0.000 $F = 5.261$, 21.627 respectively). TTPP and PCT related to neonatal blood pH and caused low neonatal blood pH ($p = 0.000$, 0.001 $F = 24.351$, 11.162 respectively). The physical and neurological development of the babies at 2, 4, 6 and 12 months follow-up, were normal and there were no congenital abnormalities in either group. TTPP relating to fetal outcome, the longer the TTPP, the worse the fetal outcome, so we should diagnose early and treat *P. falciparum* malaria in pregnancy to prevent fetal jeopardy. Artesunate with mefloquine could shorten the PCT more than quinine sulfate in pregnancy, so the fetal outcome was better than that of quinine sulfate. In cases of prolonged infection before treatment, artesunate might be the alternative treatment of *P. falciparum* malaria in pregnancy. However, its safety should be carefully studied further with a larger sample size.

Key word : Artesunate, Quinine, Falciparum Malaria, Pregnancy

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The current standard first line drug for uncomplicated falciparum malaria in non pregnant patients is a combination of mefloquine combined with artesunate[1]. Whereas, the treatment of multi-drug resistant *P. falciparum* malaria for pregnant women is quinine. Quinine is safer to the fetus than artesunate, because the former has been used for a long time. However, it takes a longer parasitic clearing time. So in the past, *P. falciparum* malaria infection of pregnant patients was associated with significant maternal and fetal mortality and morbidity[2]. An oral-form of artesunate has been the most widely used[3,4]. Its safety and efficacy have been extensively documented in non pregnant patients[5]. However, there are few reports on the use of artesunate (Qinghaosu) and its derivatives during pregnancy[6-9]. Although there is no evidence of teratogenicity or mutagenicity of these drugs,[2] the fetal resorption in rats, at relatively low doses (28 to 223 mg/kg/day) given orally on days 9 to 14 of gestation, has been reported[10,11]. We report the results of treatment with artesunate and mefloquine compared to that with quinine in pregnant women who were monitored carefully and followed-up from the day drugs were given until over one year later.

MATERIAL AND METHOD

The prospective study was conducted between January 1995 and December 1998 at the antenatal clinic (ANC), obstetrics ward and medical ward of Srisangwal Hospital. The sample size was calculated by Epi-Info Version 6.04. All *P. falciparum* malaria infected pregnant women were recruited for study by inclusion and exclusion criteria as follows.

Inclusion criteria

1. The pregnant women with a gestational age of at least 28 weeks were infected by *P. falciparum* malaria.
2. Not more than 4 per cent of parasitized red cells.
3. Can be followed-up at Srisangwal Hospital.
4. The patients could take as well as tolerate the oral form of the medicine* and be admitted to the hospital for at least 7 days.

Exclusion criteria

1. Former medication with quinine, artesunate (including its derivatives), or mefloquine within 28 days.
2. Having a history of quinine, artesunate or mefloquine allergy.
3. Malaria with complications such as shock, renal failure, pulmonary edema, cerebral malaria.
5. Mixed malarial infection.

Of 16,759 cases of malarial infection in Srisangwal Hospital during the study, 4,993 females infected by *P. falciparum* 60 of 101 cases of *P. falciparum* malaria infected pregnant women were recruited by inclusion and exclusion criteria. All subjects were informed and counseled about risks and benefits of both treatments before they voluntarily provided written informed consent. The cases were divided into two groups by a randomized method. Group I was patients treated by quinine sulfate 10 mg/kg every 8 hours for at least 7 days until the patients had clinically recovered. Group II was patients treated by oral artesunate 2 mg/kg for the first dose, 1 mg/kg every 12 hours orally for 5 days minimally, however, the treatment might be extended until the parasites were absent and the patients had clinical improvement. Mefloquine 25 mg/kg, split on day 6, was 15 mg/kg and 6 hours later 10 mg/kg orally[12,13]. Clinical and obstetric history were also recorded and a complete clinical examination was performed during the time of study. An estimate of gestational age at enrollment was made from the woman's history (last menstruation), assessment of fundal height and using ultrasonography to confirm the gestational age exactly by calculating from BPD (Biparietal diameter)[13], and calcification of placenta was also identified. Complete blood count, and thick blood films were performed on the day of admission and every day during the study. Parasite count was determined on Wright – stains thick blood films as the number of

* Every drug administration in all cases was observed by the nurses in the hospital. If vomiting occurred before 30 minutes, drug administration with a full dose was repeated. If vomiting occurred after 30 and 60 minutes half the dose was repeated. No re-treatment was given to patients vomiting after 60 minutes. The capacity of oral drug taking was evaluated after taking the medicine twice. If they vomited before 30 minutes after taking the medicine twice, they were excluded from the study.

parasites per 200 white blood cells. All patients were followed-up daily until blood smears were negative for malarial parasites and there were no clinical symptoms or signs for 3 consecutive days. They were followed-up weekly in the antenatal clinic (ANC) for at least 42 days. After this 6 week period, routine ANC follow-up was continued weekly until delivery. Treatment failure was defined as the reappearance of parasites in the peripheral blood within 42 days after treatment. This included a weekly clinical assessment of blood smear, temperature, weight and fortnightly haematocrit. To assess the treatment efficacy, we evaluated the parasite and fever clearance time (PCT, FCT), total time of parasite presentation (TTPP) (From the participants' history, we estimated the day on which the participants had begun a fever as the first day of parasite presentation). Any pregnant women complaining of fever or illness at any time, had a clinical and blood examination. The fetal growth was assessed by measuring BPD, HC (head circumference), AC (abdominal circumference), HC/AC ratio and comparing them with the normal growth curve of an intra-uterine Thai fetus by using 2SD of the normal curve[15-17] as the cut off point. The IUGR (intrauterine growth retard) was diagnosed by using the ratio of HC/AC which was less than – 2SD. Placentas will be evaluated and identified the presence of calcification by ultrasonography. Complications were recorded during pregnancy. When any abnormalities were detected, they would be treated by an obstetrician and an internist. Because the neurotoxicity of artemisinin derivatives has been shown in animals[18,19], a neurological examination including Romberg's test, assessment of heel - toe ataxia, fine finger dexterity (ability to pick up a tablet or rapid sequential finger touching), auditory acuity (using a 256 Hz tuning fork), and assessment for the presence of nystagmus, were performed weekly in every patient. All of the cases were admitted when they had uterine contractions and delivered by an obstetrician. The birthweight was recorded within 24 hours. ANC attendance and delivery details were recorded on the patient's medical records. The apgar scores, arterial cord pH at birth (collected from two-ended clamping of the umblical cord), were recorded. Meanwhile, the placenta was sent for pathological examination after delivery. Neurological assessment of tone, head control and tremor, were performed in all newborns. After birth, the children were seen monthly for 12 to 24 months to assess their physical and neurological development by the Denver developmental screening test[20]. The outcome of the two groups was compared. Analysis of variance, paired, unpaired *t*-test and chi-square test were used to examine the difference of treatment of the two groups by using the statistic program SPSS V.9.0 for Windows. P value, less than 0.05 for unpaired *t*-test and less than 0.001 for one way ANOVA, was considered significant.

RESULTS

Sixty of the second and third trimester pregnant women were infected with *P. falciparum* malaria. The 57 (95%) preganacies resulted in live births, one case in group I and two cases in group II, were lost to follow-up before delivery. By randomization there were 29 women in group I and 28 women in group II.

The general characteristics of the two groups of pateints, ($p>0.05$), before treatment were not different. The treatment results of the two groups were compared. After treatment the hematocrit in group I was less than in group II. The fever and parasite clearance times (FCT, PCT) of group II were significantly shorter than group I as in Table 2 ($p = 0.000$). None of the patients in both groups had recrudescence within 28 days.

Adverse drug effects, except for palpitations blurred vision and neonatal jaundice, were significantly different between group I and group II Table 3 (Group I had more adverse effects than group II). Of 189 neurological tests performed in 28 artesunate exposures, no adverse neurological effects were revealed.

Birthweight, arterial blood cord pH and Apgar score at 1 min in group I were less than group II ($p < 0.05$) but gestational age at birth and Apgar score at 5 min were not different between the two groups ($p > 0.05$). Fetal growth of both groups, assessed by ultrasonography, could not reveal any significant differences in the number of asymmetrical intrauterine growth retard (IUGR) and placental calcification ($p = 0.363$, 0.964 respectively) Table 5.

Parasite clearance times (PCT), after treatment, were not different between the calcified placenta and non calcified placenta group ($p = 0.058$), but there was a significant difference in total time of parasite presentation (TTPP) in the blood ($p = 0.000$) Table 6.

Table 1. Patients' characteristics.

Patients' characteristics before treatment	Means		Unpaired *t*-test	p-value
	Group I (N = 29)	Group II (N = 28)		
-Maternal age (years)	27.207	26.143	0.552	0.583
-Parity (no)	1.5862	1.357	1.271	0.209
-Height (cm)	156.75	155.107	1.509	0.137
-Weight before pregnancy (kg)	58.724	57.107	1.473	0.147
-Gestational age (weeks)	27.414	26.714	0.348	0.73
-Parasite count /200 WBC.	1,313.35	1,329.68	-0.294	0.77
-Hematocrit (%)	35.172	34.286	0.72	0.474
-Days before treatment	2.3448	2.8214	-1.235	0.222
-Degree of fever (^{o} C)	40.5517	40.3924	-1.186	0.241

Table 2. Difference of hematocrit, fever and parasite clearance times between the two groups at the end of treatment.

	Mean		Unpaired *t*-test	p-value
	Group I	Group II		
Hematocrit (%)	28.41	33.214	-4.831	0.000
TTPP (day)	9.3793	6.2857	5.245	0.000
PCT (day)	7.0345	3.4643	11.783	0.000
FCT (day)	8.04	4.47	11.809	0.000

Table 3. Adverse effects[21].

Side effects	Group I (N = 29)	Group II (N = 28)	X^2	p-value
Nausea	27	16	72.814	0.000
Vomiting	28	12	83.345	0.000
Vertigo	20	12	66.29	0.000
Tinitus	23	18	63.732	0.000
Palpitation	12	6	26.66	0.271
Blurring vision	6	11	25.953	0.305
Hypoglycemia	21	3	86.198	0.000
Neonatal jaundice	5	1	2.826	0.093

Table 4. Fetal outcome of the two groups.

Outcome	Means		*t*-test value	p-value
	Group I	Group II		
Birthweight	2,785.00	2,925.18	-2.096	0.041
Gestational age at birth	38.65	38.67	-0.073	0.491
Arterial blood cord pH	7.3428	7.3925	-2.059	0.038
Apgar score at 1 min.	8.7586	9.7143	-2.936	0.005
Apgar score at 5 min.	9.9310	10.00	-1.415	0.163

Table 5. Relationship of calcified placenta, IUGR and drug of treatment.

	Calcified placenta		X^2	p-value
	Yes	No		
Group I	3	26	0.002	0.964
GroupII	3	25		
	IUGR (Intrauterine growth retard)			
	Yes	No		
Group I	2	27	0.83	0.363
Group II	4	24		

Table 6. Relationship of TTPP, PCT and calcified placenta cases.

	Calcified placenta		Unpaired *t*-test	p-value
	Yes	No		
TTPP (day)	11.5	7.43	-3.908	0.000
PCT (day)	6.83	5.04	-1.935	0.058

Table 7. Relationship of TTPP and birth asphyxia.

	Birth asphyxia*		Unpaired *t*-test	p-value
	Yes	No		
TTPP (day)	12.6	6.8511	-10.484	0.000

*Birth asphyxia is defined by the apgar score being less than seven.

There was difference of the total time of parasite presentation (TTPP) in the group with birth asphyxia and that without birth asphyxia Table 7 ($p = 0.000$). Furthermore, by using one-way ANOVA to analyse the causes of low apgar scores at 1 min, it was found that TTPP was one of the causes of birth asphyxia ($F = 21.627$, $p = 0.000$).

To confirm the accuracy of cases which had birth asphyxia, Apgar score was less than 8, as shown in Table 8. So cases with asphyxia had less neonatal arterial blood cord pH than cases without asphyxia.

Using unpaired *t*-test and F test by one-way ANOVA to prove the relationship of duration of TTPP, PCT with neonatal acidosis and neonatal arterial blood pH, it revealed that there was a relationship as shown in Table 9. By using one way ANOVA, PCT and TTPP should be the causes of low neonatal blood pH. ($F = 24.351$, 11.162, $p = 0.000$, 0.001 respectively), especially TTPP which was more significant than PCT.

Arterial blood pH in group I was slightly less than in group II Table 10. ($p = 0.044$). The physical and neurological development of the babies for 12 months were normal in both groups. There were no congenital abnormalities in any of the newborns in this study, and all 46 children followed-up for more than 1 year, developed normally.

The birth weight of cases with calcified placenta was less than those without calcified placenta. ($p = 0.002$). TTPP was related to low birth weight ($p = 0.000$) as shown in Table 12 but there was no significant difference between TTPP and hypoglycemia or neonatal jaundice ($p =$, 0.062, 0.42 respectively) Table 13. Furthermore, TTPP was the cause of low birth weight when we used one way ANOVA ($F = 5.261$, $p = 0.000$).

Table 8. Relationship of birth asphyxia and neonatal arterial blood cord pH.

	Birth asphyxia		Unpaired *t*-test	p-value
	Yes	No		
Means of neonatal arterial blood cord pH	7.029	7.271	14.931	0.000

Table 9. Relationship of numbers of duration of TTPP and PCT with neonatal acidosis.

	Neonatal acidosis		Unpaired *t*-test	p-value
	Yes	No		
TTPP	12.09	6.85	-9.023	0.000
PCT	7.63	4.717	-4.836	0.000

Neonatal acidosis is defined by evaluation of a newborn's arterial blood pH, less than 7.10[22]

Table 10. Difference of neonatal arterial blood pH in the two groups.

	Mean		Unpaired *t*-test	p-value
	Group I	Group II		
Neonatal arterial blood cord pH	7.2017	7.2568	-2.059	0.044

Table 11. Relationship of neonatal birth weight and calcified placenta.

	Calcified placenta		Unpaired *t*-test	p-value
	Yes	No		
-Neonatal birth weight	2553.33	2889.2457	3.237	0.002

By using unpaired *t* test, neonatal jaundice related to gestational age at the beginning of the treatment ($p = 0.001$). However, when comparing the significance of the two groups, we discovered that the gestational age in group I was significantly related to neonatal jaundice ($p = 0.000$) but there was no relationship in group II ($p = 0.183$) Table 14.

DISCUSSION

The confounding factors were controlled by randomized sampling of the two groups. The general characteristics before treatment were not different between the two groups as shown in Table 1 ($p > 0.05$) but difference was observed after treatment. In this study, after treatment there were differences between the two groups concerning hematocrit value, fetal outcomes, duration of parasite presentation in blood smears. The mean hematocrit in group I was lower than in group II because group I took longer to eliminate the parasites than group II. We also found that cases which had a longer parasite presenting time, had more neonatal acidosis, more birth asphyxia, lower birth weight and more placental calcification. TTPP of longer than 12 days, related to neonatal acidosis, birth asphyxia, low birth weight and placental calcification. Placental calcification did not relate to the drug of treatment (group I and group II), but was related to TTPP, and not

Table 12. The relationship of TTPP and low birth weight.

	Low birth weight*		Unpaired *t*-test	p-value
	Yes	No		
-TTPP	13.2	7.3462	-5.834	0.000

*Low birth weight means < 2,500 g.

Table 13. Relationship of TTPP with hypoglycemia and neonatal jaundice.

	Hypoglycemia		Unpaired *t*-test	p-value
	Yes	No		
- TTPP (day)	9.125	6.9394	-3.265	0.062
	Neonatal jaundice			
	Yes	No		
-TTPP (day)	8.8	7.7692	-0.812	0.42

Table 14. Relationship of gestational age, group I, II with neonatal jaundice.

	Neonatal jaundice		Unpaired *t*-test	p-value
	Yes	No		
Mean of gestational age	37	26.12	-3.355	0.001
Mean of GA. in Group I	37	25.41	-4.974	0.000
Mean of GA. In Group II	22	27.74	1.368	0.183

GA. = Gestational age

related to PCT although this study revealed that artesunate had a shorter PCT than quinine. This study showed that TTPP in cases which had calcified placenta, was 11.5 days. PCT was 7.0345 days for quinine but only 3.4643 days for artesunate. So the time before treatment (TTPP-PCT) was estimated to be 4.466 days for quinine and 8.0357 days for artesunate. Therefore, in order to prevent calcified placenta formation in pregnant women who have been infected by *P. falciparum* for more than 5 days before treatment, artesunate should be the first line drug for them. On the other hand, if they have been infected for less than 4 days before treatment, they may be treated by either quinine or artesunate. In this study the gestation ages at birth were not different between the two groups but the birth weight was. When the fetal growth of both groups was assessed by ultrasonography, it revealed asymmetrical intrauterine growth retard (IUGR) and the amount of placental calcification in group I was significantly higher than in group II ($p = 0.000$, 0.000 respectively). As shown in Table 10, low birth weights were associated with placental calcification ($p = 0.002$). The reasons for this were that prolonged malarial infection caused degeneration changes in the placenta and implicated fetal intrauterine growth retard. A previous study revealed that the placenta of malarial infection appeared to be chronic inflamation of the chorionic villi due to macrophage and fibrin around the villi[23] and there was obstructive necrosis of the trophoblastic cells and calcification. In this regard, placental infarction, diffuse fibrinosis, caused by the degenerative process of malarial infection, may have caused a significant loss of pla-

cental function at the surface area (for respiratory or nutritional substrate exchange)[24,25] and contributed to a low birth weight. However, the gestational age at the time of infection was important for the birth weight. If it occurred in the third trimester, the birth weight was lower than the other trimesters[26,27]. The TTPP of cases which did not have birth asphyxia, neonatal acidosis, low birth weight, were 6.851, 6.85 and 7.43 respectively. Therefore, to prevent these complications, first we must diagnose the malarial infection as early as the first day of infection. Second, we should use the drug which can eliminate parasites rapidly such as artesunate, to treat falciparum infected pregnant women. The action of artesunate and its derivatives inhibit asexual formed parasite cell division and prevent the parasites from attaching the membrane of red blood cells so they can not infect the red blood cell[28,29]. Because of this action together with their effect of endoperoxides,[30] they can eliminate the ring forms speedily. Nowadays, quinine sulfate is still a safe and effective drug recommended for the treatment of uncomplicated *P. falciparum* malarial infected pregnant women. As this study revealed that quinine had the mean time of as much as 7 days for parasite clearing from pregnant blood so we recommended quinine to treat malaria in pregnancy for more than seven days. Moreover, quinine was not well tolerated, and had more side effects than artesunate. Quinine induced hypoglycemia is also common in pregnant women,[31] even those with uncomplicated malaria. This study also showed more hypoglycemia in the group treated by quinine than by artesunate ($p = 0.000$). The cause of hypoglycemia is, quinine has a stimulatory effect on the pancreatic beta cell[32] to secrete insulin and precipitate hypoglycemia and this effect can be suppressed by somatostatin analogue. The other side effect was neonatal jaundice. In group I, the gestational age at infection was related to neonatal jaundice, but not related in group II (group I $p = 0.000$, group II $p = 0.183$). In the quinine treated group, group I, the higher the gestatational age was, the higher the risk of neonatal jaundice[33]. There were a few difficulties in obtaining data on the safety of antimalarial drugs in the mother and the fetus that is why alternative treatments for malaria in pregnancy are progressing slowly. Although animal studies have indicated that high doses of parenteral artemether or artemisinin analogues cause an unusual pattern of selective damage to certain brain - stem nuclei,[34, 35] we did not find the effects of artesunate to jeopardise the fetuses in this study. Using the Denver Development Screening Test, neurological testing in newborns also failed to find any evidence of neurotoxicity, and all children who could be followed-up showed normal neurological development over the first year of life. On the contrary, we discovered better fetal outcomes in the newborn of group II (the artesunate treatment group) than in group I. Now a combination of artesunate and mefloquine is the standard treatment of uncomplicated *P. falciparum* infections in non pregnant patients with over 90 per cent efficacy[1]. Over two million patients worldwide have been treated with artemisinin derivatives and there are also reports describing the safety of exposed human pregnancies[7-9]. As already mentioned, artesunate can clear parasites from the blood circulation rapidly and has low toxicity,[30,36,37] therefore, it makes a much more suitable alternative than quinine which is associated with greater toxicity, notably an increased risk of hypoglycaemia, and neonatal hyperbilirubinemia in pregnancy[20]. However, the limitation of artesunate is its short half life[38], so it is necessary to use it together with mefloquine which has a long half life to prevent parasite recrudescence but it should be started just after the cessation of artesunate, because it can decrease the maximum concentration, increase the clearance and expand the volume distribution of artesunate[39].

SUMMARY

Neonatal acidosis, birth asphyxia, low birth weight and placental calcification depend on the duration of total parasite presentation. Artesunate had the efficacy to clear the parasites more rapidly than quinine and was as safe for the fetus as quinine, so it is an alternative treatment for *P. falciparum* malarial infection in pregnancy, especially in cases of prolonged infection before treatment (more than five days). There was no evidence of fetal or maternal toxicity in this study. In conclusion, artesunate with mefloquine can be used to treat *P. falciparum* malaria in pregnancy more effectively and safely than quinine. However, the number of cases in this study was small and larger studies are needed to define the true safety of the artemisinin compounds in pregnancy.

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การศึกษาสุ่มเปรียบเทียบผลการรักษามาลาเรีย ฟัลซิปารัมระหว่าง ควินีน และ อาร์ทีซูเนทร่วมกับเมโฟลควินในสตรีตั้งครรภ์

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การศึกษาเปรียบเทียบผลการรักษาและความปลอดภัยระหว่าง ควินีนและอาร์ทีซูเนท ร่วมกับเมโฟลควิน ที่โรงพยาบาลศรีสังวาลย์ จ.แม่ฮ่องสอนในการรักษาสตรีตั้งครรภ์ในไตรมาสที่ 2 และ 3 จำนวน 60 รายที่ติดเชื้อมาลาเรีย ชนิดฟัลซิปารัม แบ่งออกเป็น 2 กลุ่ม โดยกลุ่มที่ 1 จำนวน 29 รายได้รับควินีนทางปาก 10 มก./กก. ทุก 8 ชม.อย่างน้อย 7 วันและกลุ่มที่ 2 จำนวน 28 รายได้รับอาร์ทีซูเนททางปาก 2 มก./กก. ครั้งแรกและ 1 มก./กก.ทุก 12 ชม.อย่างน้อย 5 วัน และให้เมโฟลควิน หลังครั้งแรก 15 มก./กก. และ 6 ชม.ต่อมา 10 มก./กก. ตรวจเลือดเพื่อหาเวลาในการกำจัดเชื้อ (PCT), เวลาหายไข้ (FCT), เวลาทั้งหมดที่มีเชื้ออยู่ในกระแสเลือด (TTPP), ตรวจติดตามทารกในครรภ์ดูการเจริญเติบโตของทารกโดยคลื่นเสียงความถี่สูง, ภาวะแทรกซ้อนของยา, น้ำหนักทารกแรกเกิด, คะแนนแอปการ์, ค่ากรดด่างของเลือดในสายสะดือแรกเกิด, พยาธิสภาพของรก, ตรวจการเจริญทางกายภาพ และระบบประสาทของทารกอย่างน้อย 12 เดือน กลุ่มที่ 1 หลังการรักษามีความเข้มเลือดต่ำกว่ากลุ่มที่ 2 อย่างมีนัยสำคัญทางสถิติ ($p = 0.000$) กลุ่มที่ 2 มี PCT และ FCT สั้นกว่ากลุ่มที่ 1 ($p = 0.000, 0.000$) ทั้งสองกลุ่มไม่มีการดื้อยาหลังการรักษา 28 วัน กลุ่มที่ 1 มีผลข้างเคียงจากยามากกว่ากลุ่มที่ 2 ไม่มีความผิดปกติทางประสาทต่อมารดาทั้งสองกลุ่ม กลุ่มที่ 1 และที่ 2 มีจำนวนรกที่มีหินปูนเกาะและจำนวนทารกที่มีการเจริญเติบโตช้าไม่แตกต่างกัน ($p = 0.964$) แต่พบว่าทารกที่รกมีหินปูนจับกับไม่มีหินปูนจับ มี TTPP ที่ยาวนานแตกต่างกัน ($p = 0.000$) มีระยะเวลาของ PCT ไม่แตกต่างกัน ($p = 0.058$) TTPP ที่ยาวนานเป็นสาเหตุหนึ่งของทารกน้ำหนักแรกเกิดน้อย, คะแนนแอปการ์ต่ำ ($F = 5.261, 21.627$ $p = 0.000, 0.000$ ตามลำดับ) PCT และ TTPP ที่ยาวนานเป็นสาเหตุของการเป็นกรดในเลือดทารกแรกเกิด ($F = 24.351, 11.162$. $p = 0.000, 0.001$ ตามลำดับ) ทารกแรกเกิดทั้งสองกลุ่มตรวจไม่พบความพิการแต่กำเนิดและการตรวจติดตามทารกหลังเกิดอย่างน้อย 1 ปีไม่พบความผิดปกติของการเจริญเติบโตทางกายภาพและทางระบบประสาทของทารก ดังนั้น TTPP มีความสัมพันธ์กับสุขภาพทารกแรกเกิด TTPP ที่ยาวนานมีผลเสียแก่ทารก ดังนั้นการวินิจฉัย การติดเชื้อมาเลเรียที่รวดเร็วและรีบรักษาจะป้องกันไม่ให้ทารกมีผลเสียจากโรค การใช้อาร์ทีซูเนทร่วมกับเมโฟลควินสามารถลดระยะเวลาของ TTPP ลงได้มากกว่าควินีนทำให้ผลแก่ทารกดีกว่าควินีน จึงควรเลือกใช้ในหญิงตั้งครรภ์ในรายที่มีประวัติการติดเชื้อมาเลเรียฟัลซิปารัมมาเป็นเวลานานก่อนการวินิจฉัย แต่อย่างไรก็ตามควรมีการศึกษาถึงความปลอดภัยของยานี้ในทารกต่อไป

คำสำคัญ : อาร์ทีซูเนท, ควินีน, มาลาเรียชนิดฟัลซิปารัม, สตรีตั้งครรภ์

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