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Uterine Blood Flow Dynamic Changes in Sprague-Dawley Rats During Pregnancy Using Noninvasive Color Doppler Sonography

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THE present study was designed to evaluate the changes of uterine blood flow changes during pregnancy in Sprague-Dawley. Also, to investigate the clinical applicability of noninvasive color Doppler ultrasound to charactrize the uterine blood flow indices in the maternal uterine arteries in rats. Ten female rats weighing 280-300 gm were used and the Doppler indices were blood flow volume (BFV), time averaged maximum velocity (TAMV), peak systolic velocity (PSV), resistance index (RI), pulsatility index (PI), and diameter (D) of uterine arteries in rats during pregnancy. Examination of the uterine arteries started three days after breeding and continued at days 7, 14 and 18. Based on the noninvasive color doppler sonography, the BFV, TAMV, PSV were increased significantly at all-time points of the examination. On the contrary, the RI and PI decreased steadily at all-time points. The RI and PI showed a significant increase at day 20 of gestation. Altogether, these results indicate that non-invasive Doppler ultrasound parameters provide important information toward understanding changes in the vasculature and its perfusion of the uterus during the pregnancy period in rats. Furthermore, the present results would be key values for the uterine blood flow during pregnancy in Sprague-Dawley.

Key words: Non-invasive colour Doppler ultrasonography, Uterine artery Pregnancy, Rats.

Introduction

The circulatory and nutrition exchange systems during pregnancy are critical for the survival and growth of the post-implantation mammalian embryo [1]. Effective maternal-embryonic/fetal exchange needs significant increases in maternal blood flow to the uterus, which transports blood to the implantation site via the spiral arteries and the placenta's trophoblast-lined intervillous region [2]. The embryo's survival and growth during organogenesis are dependent on the passage of the vitelline circulation to the yolk sac, which might result in congenital abnormalities or embryonic mortality [3].

The maternal body is a dynamic link between the environment and the intrauterine fetus. It is important for the conceptus to grow normally and has enough exchange of oxygen, nutrients, and waste products at the uteroplacental interface. They work more efficiently if the female is healthy enough to carry out the procedures [4]. In mammalian species, intrauterine hemodynamics has been thought to play a role in the variation of placental and fetal weights between litters [5, 6].

The rat has several benefits over mice and other creatures as a model of human disease. Actually, rats were previously the most commonly utilized creature in medical research.

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The rat is a perfect model for cardiovascular disorders, specifically stroke and hypertension, and a variety of genetic stocks are available for these investigations [7]. The physiology of the rat is easier to observe, and an amount of available data has developed over time that would take years to be recreated in the mouse [8]. Furthermore, in many circumstances, the physiology closely resembles the human condition. The rat is preferable to other models in studies of cognition and memory as the physiological systems involved in learning and memory have been thoroughly researched in this animal. The rat can learn a wider range of activities significant in cognitive study. Because of the proportional size of critical substructures in organs, which influences both how much of the organ is involved in an experimental lesion and the distance effects of medication delivery to specific anatomical locations, the size of the animal improves its value as a disease model [8, 9]. For mechanistic studies of human reproduction, the rat is the most commonly used model. Because of the rat's size, serial blood draws are possible in pharmacological investigations [10] Physiology, pathology, pharmacology, toxicology, and transplantation investigations using the laboratory rat as a model. Because practically every medicine approved for human therapy passes through the bodies of laboratory rats, pharmacological research is extremely valuable. Hundreds of different rat models have been created to replicate pathological and physiological human clinical circumstances, particularly in complicated disorders [10]. Many of the model rats are deposited in rat resource centers, where biomedical researchers can use and share animals and rat-related resources. Traditional transgenesis, chemical ENU mutagenesis, and transposon insertional mutagenesis, among other recent advances in genetically altered rat technologies, will give hundreds of relevant rat models for functional genomics and human disorders. Rat resource centers that operate on a global scale are essential for successful and long-term research in the biomedical sector that uses rats as a model species [11, 12]. Unlike mice, rats are easy to handle and less easily stressed by human contact [13]. Accordingly, the aim of the current study is to use the non-invasive color Doppler ultrasound to follow the heamodynemic changes of the uterine arteries blood flow during pregnancy in rats. Secondly, figure out a reference qualitative and quantitative assessment of uterine arteries blood flow changes during pregnancy in rats as an experimental model for human beings.

Methods

Experimental animals

This study was carried out in strict accordance with the recommendations of Institutional animal care and use committee (IACUC). The experimental procedures were approved by the Animal Care Committee of the faculty of veterinary medicine, Mansoura University (M/162). Ten female Sprague-Dawley rats (Medical research center, faculty of medicine, Mansoura University) weighing 225–250 g were mated with a known fertile male. The presence of spermatozoa in morning vaginal smears was used to determine the first day of pregnancy. All animals were kept in cages with controlled lighting from 6 a.m. to 6 p.m. The dams were inspected by the same person (Mariam Rabie) using noninvasive colour Doppler ultrasound. All animals were housed under controlled lighting (6 AM–6 PM). The dams were examined by noninvasive color Doppler ultrasound by the same person (Mariam Rabie). All examinations were performed using the same ultrasound machine (Esaote MyLab 30X Vision, Esaote, Genova, Italy) with multi-frequency probe (6-12) with a filter of 100 Hz, power of 50%, pulse repetition frequency (PRF) of 4,500 Hz, and Doppler angle ranging from 0 to 40.

Doppler ultrasound imaging and location of the uterine arteries

The investigations with Doppler exhibited that the uterine arteries in the pregnant rats were located in all experimental rats Uterine arteries in the pregnant rats were located in all experimental rats. Doppler signals in the uterine artery close to the lateral-inferior margin of the utero-cervical junction near to the internal iliac artery on either side. They were examined and assessed transabdominally as previously mentioned [14]. The Doppler indices were measured according to previous literatures [15, 16]. Briefly, 2 mL of ultrasound gel was applied on the abdominal skin after shaving of the hair and the lubricated transducer gently applied on the abdomen between umbilicus and two hind limbs. Uterine arteries were located cranio-lateral to the bladder (Figure 1). Imaging of the uterine artery was successful in all examinations. The duration of each examination was about 5–10 min. To evaluate the volume of blood flow, the insonation angle was adjusted between 0 and 30°.

Doppler indices of uterine arterial blood flow in this study of the rats during pregnancy included uterine artery diameter (DM), Peak systolic velocity (PSV), time averaged maximum velocity (TAMV), blood flow volume (BFV), Resistance index (RI) and pulsatility index (PI) Ultrasound examinations were done every 3 days beginning on Day3 (after detection of spermatozoa in vaginal smear) until Day 20 (D 20).

Statistical analyses

The statistical procedures were carried out according to previous studies [16, 17]. To conduct statistical analyses, SAS® software (version 9.2, SAS Institute, Cary, NC, USA) was utilized. For all analyses, differences were deemed significant at $P \leq 0.05$. Each species' analyses were carried out independently. The Shapiro-Wilk test was employed to determine the normality of all variable distributions. A mixed model one-way analysis of variance (ANOVA) with time points as repeated measurements was used to explore the effect of day (days of pregnancy) on blood flow parameters. Doppler parameters were used as least-squares means to examine the influence of the day of pregnancy. Pearson's correlation was used to examine the correlations between Doppler measurements and postpartum days, as well as changes in uterine diameter.

Results

Changes in uterine blood flow during pregnancy in rats

As shown in Fig. 2 (A&B) and Fig. 3 (A&B), all variables (PSV, PV, TAMV, and BFV) revealed variations based on the stage of pregnancy. When comparing the initial stage to the middle stage and the final stage, PV showed no variations, however for the other aspects, differences were identified throughout all times.

The PSV, PV, TAMV, and BFV significantly increased as the gestation period progressed; an increase was observed in these parameters throughout pregnancy with maximum levels at the end of pregnancy (day 20) ($P < 0.05$). The RI decreased between days 3 and 18 ($P < 0.05$) and increased by day 20 ($P < 0.05$) to values similar to those on day 9 ($P > 0.05$) Fig. 4 (A). The PI remained constant between days 3 and 6 ($P > 0.05$) then decreased to minimal values by day 18 ($P < 0.05$) and then increased again by day 20 ($P < 0.05$) Fig. 4 (B). The diameter of the uterine artery (D) remained constant until day 9 ($P > 0.05$), then increased between days 9 and 20 ($P < 0.05$) (Fig. 5).

Correlations among various blood flow parameters in pregnant rats

In pregnant rats (Table 1), there were positive correlations ($P < 0.05$) between the following blood flow parameters: 1) BFV and TAMV, r = 0.703; 2) BFV and PSV, r = 0.660 3) BFV and D, r = 0.846. Negative correlations ($P < 0.05$) were observed between PI and other parameters including: PI and BFV, r = −0.634, PI and TAMV, r = −0.599 3) PI and PSV, r = −0.78. Further, negative correlations were investigated between RI and BFV, r= -0.719 RI and TAMV, r= -0.586 RI and PSV r= -0.76. A positive correlation also was investigated between PI and RI, r= 0.88.

Quantitative evaluation of the uterine blood flow during gestational period in rates

The quantitative assessments of the uterine artery blood flow were illustrated in fig 6 (b-h). With the advancing f the pregnancy, the thickness of the Doppler waves showed a significant increase. Moreover, the distance between the zero line and the end diastolic velocity was also increased throughout all examination time points of the pregnancy.

Discussion

Rattus norvegicus, a laboratory rat, has been used in biomedical research for more than 150 years and is frequently still the model of choice for investigations into physiology, behaviour, and complex human diseases [11]. Regarding to the use of non-invasive color Doppler ultrasound application in animal reproduction, it was proven that non-invasive ultrasound imaging is a successful method for studying the uterine artery blood flow changes during pregnancy in cows [18], small ruminants [19], buffaloes [20, 21], horses [22, 23] as well as in women [24–26].

In rats most of literatures investigated the changes in the uterine blood flow during different models either for diabetes [27, 28], preeclampsia [29, 30] or the intrauterine fetal growth retardations [30–33]. Accordingly, the results of the present study regarding the investigation of uterine blood flow changes during normal pregnancy in rats would be considered as a references values for the uterine arteries Doppler indexes variation. In the current study, the velocity Doppler indices (PSV, PV, TAMV) as well as the volume of blood flow during the pregnancy revealed different patterns depending on the stage of pregnancy. Peak velocity showed no differences when compared to the intermediate and end stages, however the other variables exhibited significant differences during different gestational times. The PSV, PV and TAMV Doppler values grew dramatically as the pregnancy proceeded; we observed an increase in these parameters throughout gestation, with the highest levels at the end of the pregnancy. The dramatic increases for these values in the present study would be attributed to the normal intrauterine fetal growth changes within the uterus as well as changes in the diameter of the uterine arteries throughout the gestational period [19]. In this manner, the investigation of BFV changes constantly throughout the length of the gestation in pregnant rats. The rise in the blood flow volume during different stages of the pregnancy is associated primarily to the growth of feoti intrauterine. As long as the intrauterine fetal growth showed normal development, there is usually a progressive increase in the uterine blood perfusion to accommodate the increasing in the size of feoti. The same results are proven in pregnant sheep and goats throughout pregnancy [19] as well as in buffaloes [20, 34, 35] , cows [36] and women [37]. The sheep is considered as the best animal model for studying the changes in uterine arteries hemodynamics in the women [38, 39]. It is noteworthy, the changes in the uterine blood flow volume during pregnancy in rats in the current study may be attributed to the development of the utero-placental circulation through the different stages of the pregnancy according to the number of feoti [19] as well as the normal intrauterine growth [39, 40]. For a long period of time the sheep studies provide the most accurate data on uterine hemodynamic changes during pregnancy. The beginning and development of the uteroplacental circulation has been characterized in two stages [37]. The first stage lasts from implantation until 0.6 of gestation (approximately 145 days) and is characterized by placental growth and development as well as the formation of new blood vessels [38]. Placental blood flow accounts for roughly 60% of total blood flow [19]. The data of the current study indicated that the rats may be used as an experimental model also for pregnancy in pregnant women. Many studies used to investigate the placental dysfunction in the human being using the pregnant rat [41–43] and mice model [44–46].

In the current study, the uterine arteries blood flow resistance and pulsatility indices (RI, PI) showed a characteristic decreasing changes during the pregnancy period in the pregnant rats. These resistance impedance Doppler parameters increased significantly close to the parturition. Furthermore, there is a significant negative correlation between the resistance impedance and the blood flow velocity Doppler parameters of the uterine arteries in the current study. These results are in the same way of the previous studies in small ruminants [19], cows [16, 36], buffaloes [20] as well as pregnant women [47, 48]. In pregnant women. The uterine vascular resistance drops dramatically throughout the equivalent period of human pregnancy [49, 50]. Continuous-wave Doppler ultrasonography found similar increases in compliance in the uterine arteries and the radial or arcuate arteries [51, 52]. A similar pattern was discovered in the arcuate arteries using a transabdominal pulsed Doppler duplex instrument. In sheep also there were published data that indicates that the second stage lasts for two months in sheep and is characterized by an exponential growth of the foetus and a significant increase in the cross-sectional area of the uterine vascular bed [19]. This is due to vascular smooth muscle hypertrophy, a decrease in the collagen component of the uterine arterial dilatation of the uteroplacental vascular bed [47].

Regarding the qualitative evaluation of the Doppler waves of the uterine arteries during pregnancy, the current study showed an increase of the distance between the zero line and the end diastolic velocity [53]. This pattern of increase indicates the normal response of the uterine arteries diameters to the increased fetal mass within the uterus. Of note, this is the first study to describe the qualitative assessment of the uterine blood flow during pregnancy in rats. In women, pulsed Doppler qualitative assessment was used In order to determine whether complications related to impaired trophoblastic invasion of the placental bed, such as pregnancy-induced hypertension, intrauterine growth retardation, and foetal asphyxia, could be predicted by this measurement, the blood flow velocity profiles in uterine vessels (arcuate arteries) at 16 to 18 weeks' gestation were assessed using a pulsed Doppler apparatus [54]. Moreover, many studies indicate the importance of qualitative assessment of the Doppler waves in the diagnosis of intrauterine fetal growth restriction [26, 55–57].

In the current study, the qualitative guideline for normal gestation in rats was illustrated. This would be used in other studies to diagnose the abnormalities during pregnancy. For more declarations.

In pregnant women with suspected severe placental insufficiency, an umbilical artery Doppler should be accessible for examination of the fetal-placental circulation [58–60]. Reduced, missing, or reversed umbilical artery end-diastolic flow is a reason for increased fetal observation or delivery, depending on other clinical considerations [61]. Umbilical artery Doppler should not be utilized as a screening technique in healthy pregnancies because it has not been demonstrated to be useful in this population [56].

In conclusion, the non-invasive color Doppler ultrasound imaging can be used as a successful safe method to follow up the hemodynamic changes of the uterine arteries in rats during pregnancy. Moreover, the results of the current study would be considered as a reference value for the normal uterine artery blood flow changes during pregnancy in rats.

Abbreviation:

BFV: Blood flow volume

D: Diameter of uterine arteries

IACUC: Institutional animal care and use mittee.

PI: Pulsatility index

PRF: pulse repetition frequency

PSV: Peak systolic velocity

PV: Peak velocity

RI: Resistance index
TAMV: Time average maximum velocity

Conflict of interest

There are no competing interests.

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Authors' contributions

Mariam Rabie: Conceptualization, Methodology, Investigation, Data curation, writing – original draft, Heba Sharawy: interpretation of Doppler data and writing of manuscript.

Mohamed El-Adl: Data curation, writing – original draft, Reviewing.

Samy Zabel: Data curation, writing – original draft, Reviewing.

Mohammed A. Elmetwally: Conceptualization, Methodology, Investigation, Data curation, Statistic analyses, Writing – original draft. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

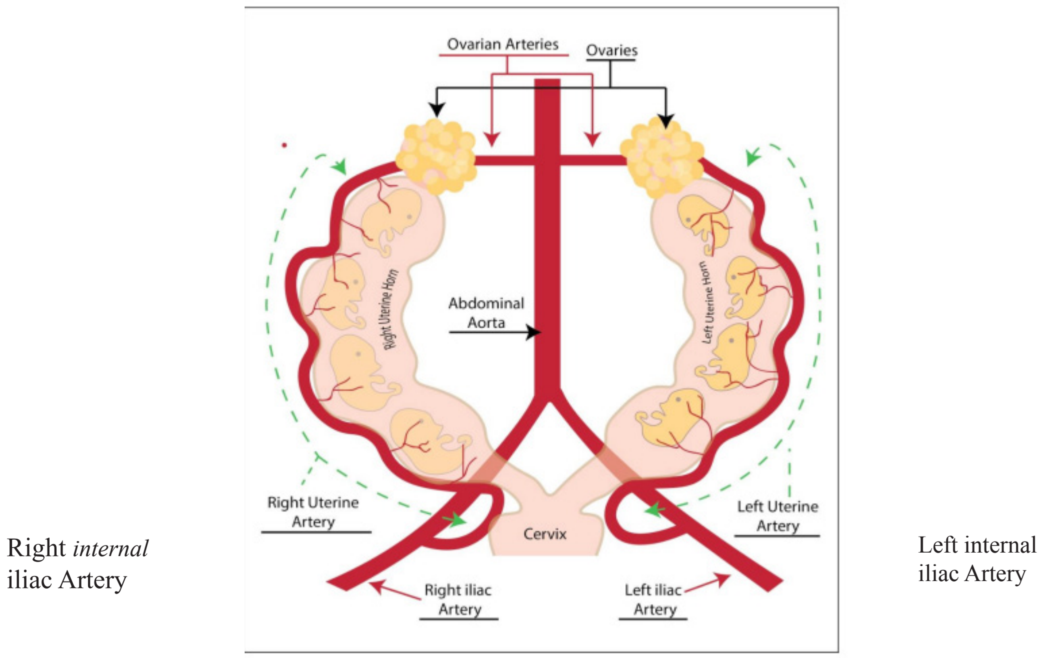

Fig. 1. Demography illustrating the uterine blood supplies in rats during pregnancy.

TABLE 1. Spearman's rank correlation coefficients for the relationships between blood flow volume (BFV), time averaged maximum velocity (TAMV), peak systolic velocity (PSV), resistance index (RI), pulsatility index (PI), and diameter (D) of uterine arteries in rats during pregnancy.

	BFV	TAMV	PSV	RI	PI	D
BFV	1	0.703**	0.660**	−0.719**	−0.634**	0.846**
BFV		0.00	0.002	0.00	0.03	0.000
TAMV	0.703**	1	0.731*	-0.586**	-0.599**	0.770*
TAMV	0.00		0.01	0.04	0.02	0.00
PSV	0.660**	0.731*	1	-0.76*	-0.78*	0.804**
PSV	0.002	0.01		0.01	0.01	0.00
RI	−0.719**	-0.586**	-0.76*	1	0.880**	-0.564*
RI	0.00	0.04	0.01		0.000	0.04
PI	−0.634**	0.599**	-0.78*	0.880**	1	-0.701**
PI	0.03	0.02	0.01	0.000		0.02
D	0.846**	0.770*	0.804**	-0.564*	-0.701**	1
D	0.00	0.00	0.00	0.04	0.02	

Bold parameters are R value and reverse bolding indicate P value.

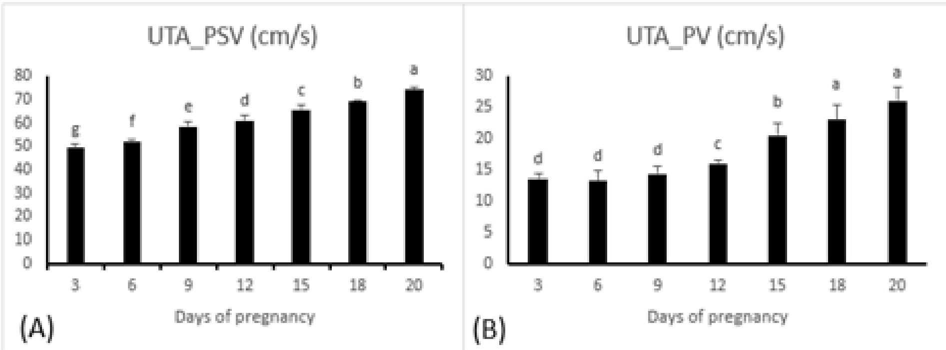

Fig. 2. Uterine artery blood flow parameters in pregnant rats throughout pregnancy (A) peak systolic velocity (PSV), (B) peak velocity (PV). Values are described by Mean ± SEM. Means with different superscripts (a, b, c, d, e, f, g) are significantly differ.

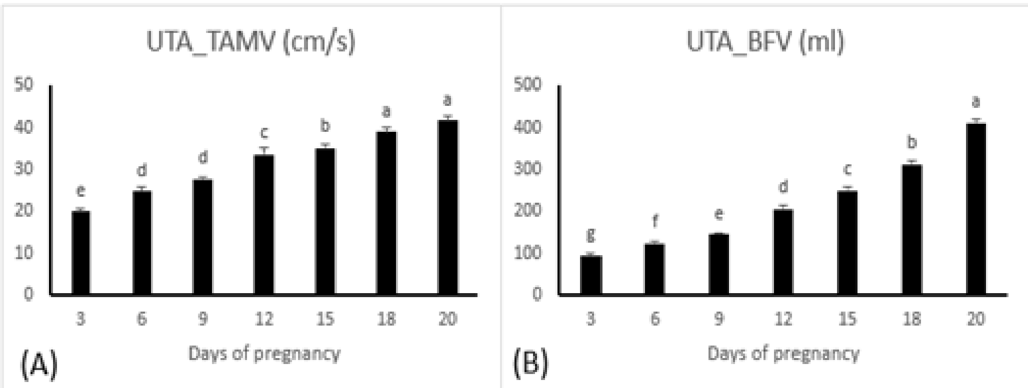

Fig 3. Uterine artery blood flow parameters in pregnant rats throughout pregnancy (A) Time average maximum velocity (TAMV), (B) Blood flow volume (BFV). Values are described by Mean ± SEM. Means with different superscripts (a, b, c, d, e, f, g) are significant.

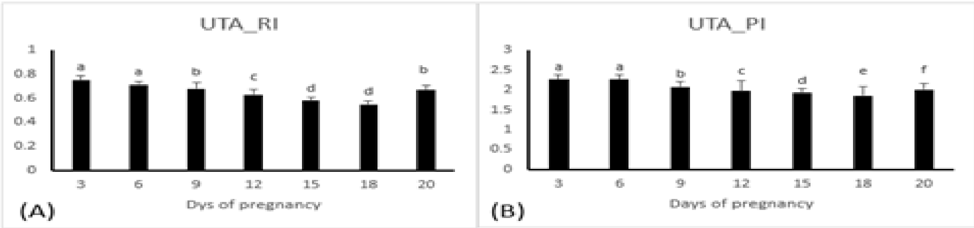

Fig 4. Uterine artery blood flow parameters in pregnant rats throughout pregnancy (A) Resistance index (RI), (B) Pulsalitary index (PI). Values are described by Mean ± SEM. Means with different superscripts (a, b, c, d, e, f) are significantly different (P < 0.05*).*

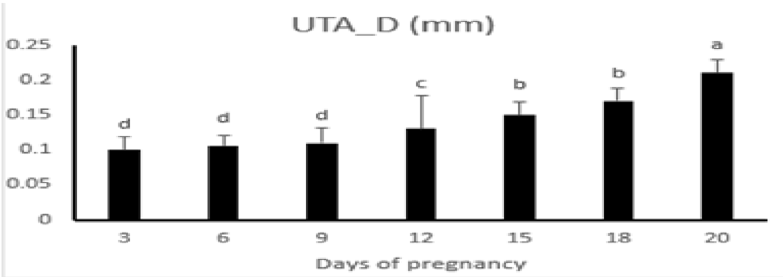

Fig. 5. Uterine artery diameter in pregnant rats throughout pregnancy. Values are described by Mean ± SEM. Means with different superscripts (a, b, c, d) are significantly different (P < 0.05).

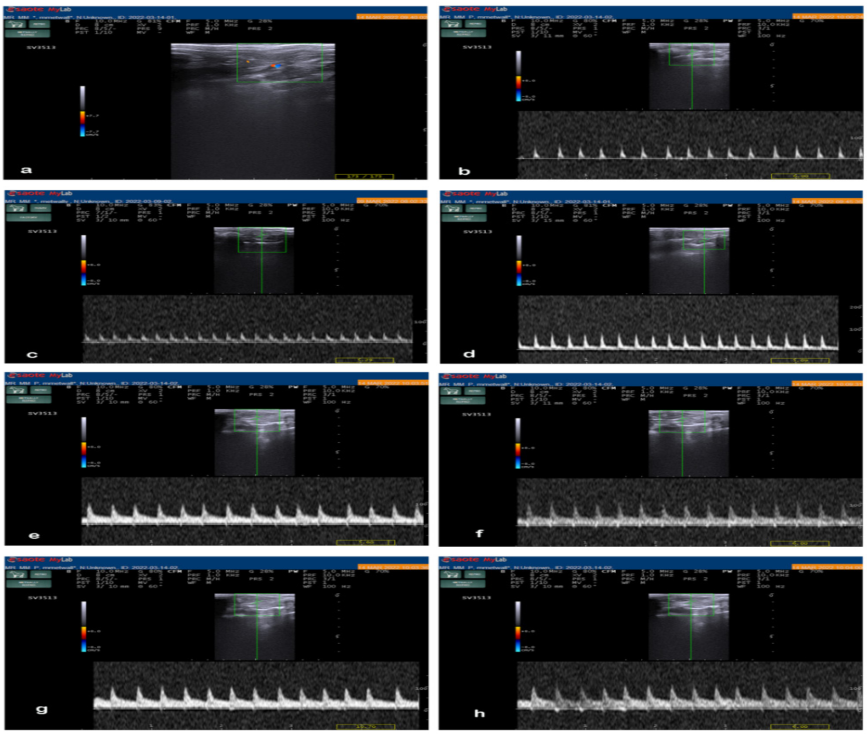

Fig. 6. Quantitative assessments of the uterine artery Doppler waves in rats during pregnancy. A: location of the uterine artery in pregnant rats; b: Doppler waves at day 3 of the pregnancy; c: Doppler waves at day 6 of the pregnancy; d: Doppler waves at day 9 of the pregnancy; e: Doppler waves at day 12 of the pregnancy; f: Doppler waves at day 15 of the pregnancy; g: Doppler waves at day 18 of the pregnancy; h: Doppler waves at day 20 of the pregnancy.

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التغيرات الديناميكية لتدفق الدم في رحم الجرذان أثناء الحمل باستخدام التصوير بالموجات فوق الصوتية دوبلر الملونة غير الباضعة

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تم تصميم الدراسة الحالية لتقييم التغيرات في تغيرات تدفق الدم في الرحم طوال فترة الحمل في الجرذان البيضاء. أيضًا لمعرفة إمكانية تطبيق التصوير بالموجات فوق الصوتية دوبلر الملونة غير الباضعة سريريا لوصف مؤشرات الدورة الدموية الرحمية في شرايين رحم الأم في الجرذان . تم استخدام عشر إناث جرذان تزن 300-280 جم وكانت مؤشرات دوبلر هي حجم تدفق الدم ، ذروة السرعة الانقباضية، مؤشر المقاومة ، متوسط السرعة القصوى للوقت ، مؤشر النبض، وقطر من الشرايين الرحمية في الجرذان أثناء الحمل. بدأ فحص الشرايين الرحمية بعد ثلاثة أيام من التكاثر واستمر في الأيام 7 و 14 و 18. استنادا إلى الموجات فوق الصوتية دوبلر الملونة غير الغازية ، تم زيادة حجم تدفق الدم ، متوسط السرعة القصوى للوقت ، ذروة السرعة الانقباضية بشكل ملحوظ في جميع نقاط الفحص. على العكس من ذلك ، انخفض مؤشر المقاومة و مؤشر النبض بشكل مطرد في جميع النقاط الزمنية. أظهر مؤشر المقاومة و مؤشر النبض زيادة كبيرة في اليوم 20 من الحمل. تظهر هذه النتائج بشكل جماعي أن قياسات التصوير بالموجات فوق الصوتية دوبلر غير الغازية توفر معلومات مهمة لفهم التغيرات في الأوعية الدموية وتروية الرحم طوال مرحلة الحمل للجرذان . علاوة على ذلك ، ستكون النتائج الحالية قيما أساسية لتدفق الدم في الرحم أثناء الحمل في الجرذان البيضاء.

الكلمات الدالة: التصوير بالموجات فوق الصوتية دوبلر الملونة غير الغازية ، حمل الشريان الرحمي ، الجرذان