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The Effects of Shock Waves on the Rat Fetus

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Abstract: There is an ongoing controversy regarding shock wave lithotripsy (SWL) contraindicated during pregnancy (1, 2). While the effects of shock waves on a variety of cells in both clinical and experimental studies are well documented, their effects on the fetus remain to be clarified. In this study, we investigated the effects of SWL on the rat fetus. On the 8th, 11th, 14th and 17th days of pregnancy, 100, 250 or 500 shock waves were produced with a Multimed 2001 ELMED Systems Lithotriptor. In ongoing pregnancy, the effects of SWL on fetuses ranged from mild in early pregnancy to moderate and fatal later. No viable fetuses were determined in the latest period of pregnancy in rats taking 500 shocks. Histological changes were observed in the brain, lungs and subcutaneous tissue. Fusion and necrosis were determined in many of the dead fetuses.

Our study demonstrates that SWL causes fetal damage and death during the late period of pregnancy in rats. Additional studies on the use of SWL during pregnancy mustbe done with later-generation lithotriptors.

Key Words: SWL, pregnancy, rat.

Introduction

SWL is currently an outpatient procedure administered with minimal or no anesthesia. Moreover, SWL has rapid acceptance and adaptation by patients because of the false perception that this technology is entirely safe and that shock-wave treatment does not induce severe acute and chronic side effects. However, numerous clinical and experimental reports present evidence that SWL can cause severe acute effects (3, 4, 5). The changes are commonly seen in the kidney and associated tissues, but also in the liver, pancreas, skeletal muscles and gastrointestinal tract. The effects of shock waves on the fetus and pregnancy is another matter of controversy. Pregnant patients may have non-obstetrical abdominal pain due to calculi (6). It is estimated that 1:188 to 1:3,821 of all pregnancies are complicated by kidney stones (7, 8). The diagnosis and treatment of a stone are equally difficult (9, 10). SWL by ultrasonic visualisation would be an important treatment option. This calls for thoroughly planned clinical trials as well as carefully controlled experimental studies conducted on animal model systems in vivo and in vitro (11, 12). We studied the effects of shock waves on rat fetuses at multiple stages of pregnancy.

Materials and Methods

In this study, female Swiss albino rats were used. They were paired with male rats and on the following day rats with a vaginal plug were accepted as pregnant. This was the first day postcoitum. On the 8th, 11th, 14th and 17th days of pregnancy they were exposed to 100, 250 and 500 shock waves. We divided 80 rats into four groups:

Group I a- 100 shock waves were applied
b- 250 shock waves were applied
c- 500 shock waves were applied
d- Control group.

(On the 8th day of pregnancy)

Group II a- 100 shock waves were applied
b- 250 shock waves were applied
c- 500 shock waves were applied
d- Control

(On the 11th day of pregnancy)

Group III a- 100 shock waves were applied

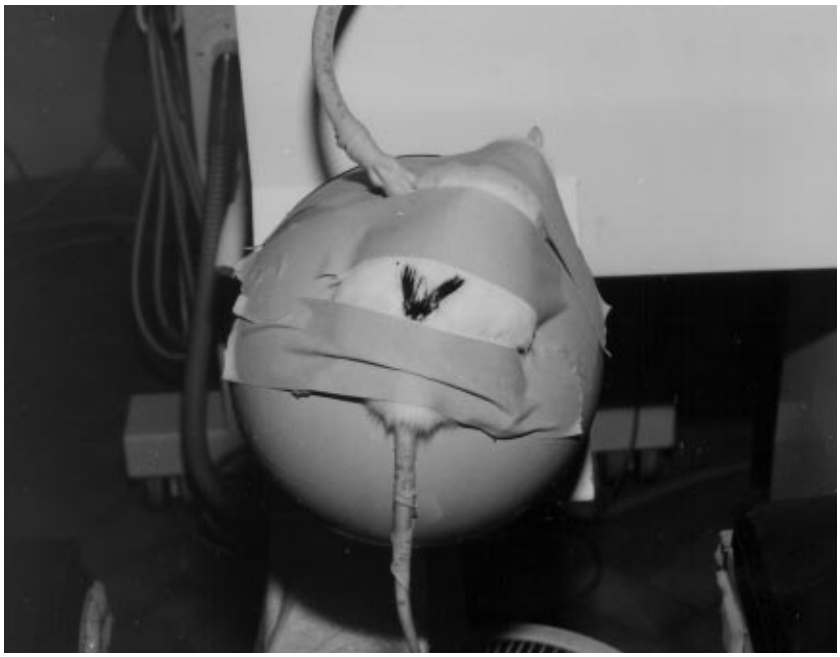


Figure 1. Anaesthetised rat on the flexible membrane of the lithotriptor.

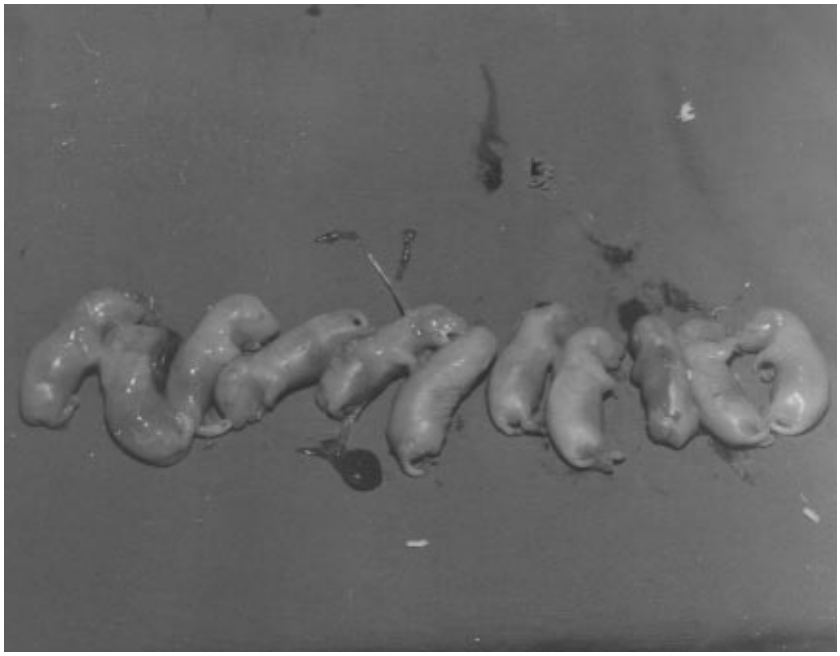


Figure 2. Fetuses with evident subcutaneous hematomes.

b- 250 shock waves wereapplied

c- 500 shock waves were applied

d- Control

(On the 14th day of pregnancy)

Group IV a- 100 shock waves were applied

b- 250 shock waves were applied

c- 500 shock waves were applied

d- Control

(At 17th day of pregnancy)

A Multimed 2001, ELMED lithotripsy systems, second generation shock wave lithotriptor, was used in study. Shock waves were produced at one shock per second of 20 kV.

They were anaesthetised with 50 mg/kg intramusculer ketamine HCL before SWL. Anaesthetised rats were placed on the flexible membrane of the lithotriptor. Their abdomens were fixed on the membrane

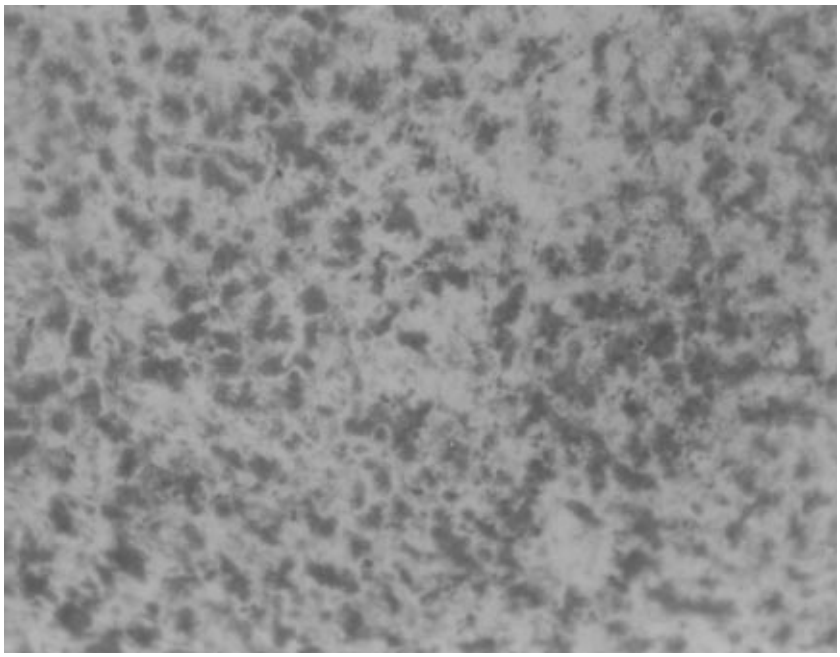
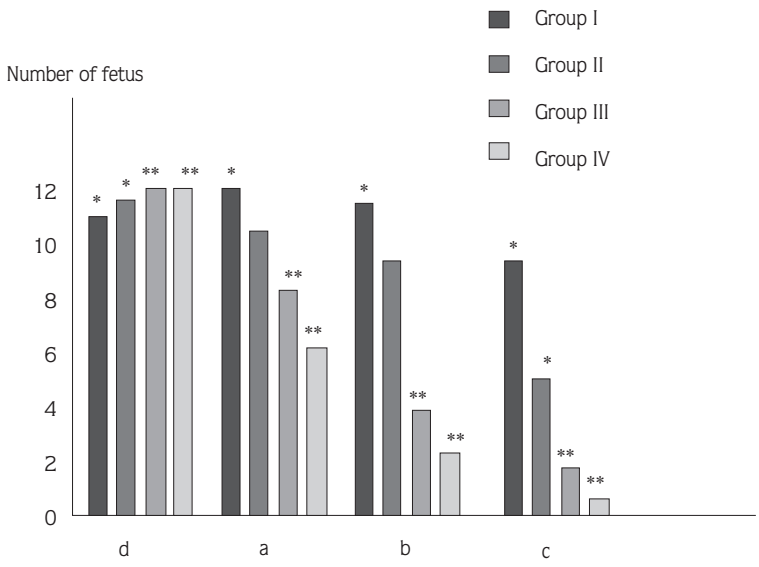


Figure 3. Fetal liver necrosis (H+E, X33)

Table 1. Mean number of viable fetuses.



*P>0.05

with adhesive tape, and echo-jelly was applied between abdomen and membrane for good acustic coupling (Figure 1). They were placed accurately at the range of the second focus of the shock wave generator by focus collimator. The focus collimator pointed the centre of the F2 into the space. The flexible membrane was expanded to 15mm below the centrer point at the F2, so that the distance from the suggested stone surface to the bifurcation of the uterus was considered to be 15mm. They received equal amounts of shock waves to the four quadrants of the abdomen (25 shock waves eachfor a total of 100 shock waves, 63 for a total of 254 and 125 for a total of 500). For the control group, rats were placed on the membrane after anesthesia and focused but were not exposed to shock waves.

On the 18th day postcoitum, midline vertical laparotomy was performed on the living rats under ketamine HCL anesthesia, and the fetuses were removed. After each shock wave exposure, two rats from each group were killed and acute effects were observed.

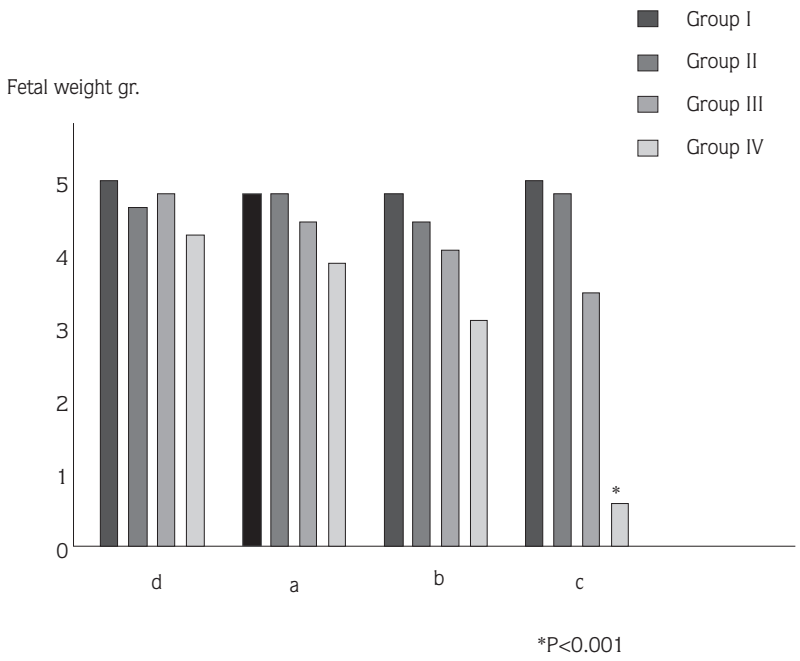


Figure 2. Mean fetal weights

Table 3. Maternal effects.

Group	Observed pathology
2b	Congestion in the kidney
2c	Congestion in the kidney, lungs and spleen Tiny foci of hemorrhage in the lungs.
3c	Marked congestion in the kidney and liver. Petechial bleeding and patch necrosis in the liver.
4c	Marked congestion in the spleen and liver Turbulan dilation and cast formation in the kidney. Petechial bleeding in the intestine.

Histological examination was performed on each. Fetal viability was checked by fetal movement or presence of heart beat. Fetuses were weighed and any macroscopic anomalies present were noted. Finally, all removed fetuses were fixed in Bouin's solution and stained with hemotoxylin and eosin. Test and control animals were compared statistically using the paired Students't test.

Results

Fetal and uterine effects: Table I shows the average number of viable fetuses ineach group. According to table I, there was no statistically meaningful difference between control rats and rats exposed to shock waves in group-I ($P>0.05$). In groups IIa and IIb the viability rate was lower than in the control group. In group IIc, the viability rate was half that of the control group ($P<0.05$). IIIa, b, c and IVa, b and c the fetal viability rate decreased in proportion to the increasing shock wave number. Moreover, in group IVc, to which 500 shock waves were applied, no fetuses survived ($P<0.001$). Table II represents the relation between fetal weight and viability. It was determined that in all groups except IVc, viable fetus weight were similar to each other and there was no statistically meaningful difference. In group IVc, however, the mean fetal weight was statistically different from that of the control group ($P<0.001$). No macroscopic difference was observed among the uteri in groups I, II, III, a, b, c and the control groups. In groups IVb and IVc, many dead fetuses, some almost reabsorbed and fused, were found in the uteri. Macroscopic examination of viable fetuses revealed no anomalies in any group, but there were evident subcutaneous hematomas (Figure 2). Histopathologic examination of the uterus revealed no difference between experimental and control group. In histologic examination after treatment, no histologic effects were determined in groups I, II, III a, b and c. But in groups IVb and IVc, subcutaneous, abdominal and lung hemorrhages were found, and fetal liver necrosis was found in one (Figure 3).

Maternal effects: All of the adult rats survived. No significant morbidity was observed. No abortions were noted. No significant morbidity was observed. No abortions were noted. Observed histopathologic changes

are shown in Table 3.

Discussion

SWL is clearly an effective non-invasive treatment for a wide variety of urinary tract calculi. Nonetheless, several experimental studies have demonstrated vascular injury and tisue trauma after high energy shock wave exposure (13, 14). However, even in animal experiments, only transient renal injury (without hematoma) is observed if the experimental conditions are comparable to those used in clinical routine (15). Perirenal and intrarenal hematomas are rare clinically, as supported by the fact that only 50% of the patients undergoing SWL demonstrate a mild and transient increase in c-reactive protein, which is a marker of tissue lesions (15). No long term significant damage to the kidney or surrounding organs has been shown to detract from the overwhelming positive benefits of lithotripsy (16). Furthermore, extensive longer-term stduies exceeding 5 years have shown only slight increases in diastolic blood pressure among patients treated with SWL, the significance of which is unclear (17). Additionally, with later generation lithotriptors significantly fewer shock waves and shorter treatment times due to a narrow shock wave focal point are needed to complete stone fragmentation (16). But the effects of this treatment on the fetus remain to be ascertained, and extracorporeal shock wave lithotripsy during pregnancy is generally not advised (1, 2). The effect of shock waves on the fetus was the question which prompted this study. There have been some studies on this subject, but the effects of shock waves at different stages of pregnancy have been little discussed. Moreover, this study provides additional information for the further investigations using a model closer to humans. The rat model was chosen because of the relative ease of obtaining large numbers of accurately-timed pregnant animals.

Smith et al. used the rat model to determine the effects of SWL, but only at day 9 of gestation. They did not report any recognizable gross or microscopic fetal damage (11). In an another study, Ohmari et al. reported the effeacts of SWL during the late stage of pregnancy but on mouse fetuses. They also used a second generation lithotriptor and their results closely resembled our (12). Additionally in our study, in group 4c, the 18th day-plus, 500 shock-wave group, no viable fetus was determined, and in group 3c, the mean viable fetal weight was half that of the control. It is thus evident that shock waves caused fetal damage and affected fetal development. Furthermore, histopathological examination of the fetuses revealed hemorrhages in the kidney, lung, liver and subcutaneous tissue due to vascular trauma from the shock waves. It should be remembered that 500 shocks on the target not beyond 15mm are not the therapeutic dose for stones in the urinary system. Hunter et al. reported an 80% reduction in shock wave pressures in an area extending 10 - 15mm from the f2 point, but also noted stone fragmentation well beyond f2 in the axial plane. He named this extended region of effectiveness the "blats path" (18). This may explain the observed histopathologic changes and vascular trauma of shock waves over a 15mm area of the rat's pelvis in our study. Moreover, we did not investigate the chronic effects of shock waves on fetuses. But in previous reports based on animal studies, chronic changes (1 to 2 months) in the bones including aseptic marrow necrosis, damage to osteocytes, and evidence of bone remodiling of 20 kV intensity were determined (19).

As a result, urolithiasis during pregnancy is usually an acutely painful complication which may require ureterorenal draining by endoscopic or percutaneous methods (20). Urinary infection and intolerance of drainage stents can occur. But SWL was not safe, especially after the first trimester. Endourologic treatment by laser lithotriptors or SWL by new-

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