Asian Journal of Health Research
Journal Homepage: https://a-jhr.com
Published by Ikatan Dokter Indonesia Wilayah Jawa Timur

Systematic Review

Elevated Blood Pressure in Rat Offspring with Induced Intrauterine Growth Restriction: A Systematic Review

Geneung Patridina*, Nugrahanti Prasetyorini

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya/ dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia

ARTICLE HISTORY
Received: 14 May 2025
Revised: 12 June 2025
Accepted: 24 July 2025

CORRESPONDING AUTHOR*
Geneung Patridina
gpatridina@gmail.com
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya/ dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia

KEYWORDS
Intrauterine Growth Restriction (IUGR); Rats; Placental Insufficiency; Blood Pressure

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ABSTRACT

Introduction: Intrauterine growth restriction (IUGR), often caused by placental insufficiency, is a significant obstetric issue associated with adverse long-term health outcomes, including hypertension. This systematic review investigates the association between induced IUGR and elevated blood pressure in rat offspring.

Material and Methods: A systematic search of PubMed, SpringerLink, and the Cochrane Library was conducted on February 10, 2023, following PRISMA guidelines. Studies were included if they involved rat models of placental insufficiency-induced IUGR with documented birth weight reduction and blood pressure measurements compared to a control group. Data were extracted for meta-analysis using Review Manager 5.

Results: Eight studies met the inclusion criteria. Meta-analysis revealed a significant increase in both mean arterial pressure (MAP) (Mean Difference: 9.84, 95% CI: 2.69–16.99, $p = 0.007$) and systolic blood pressure (SBP) (Mean Difference: 13.09, 95% CI: 7.87–18.32, $p < 0.00001$) in IUGR offspring compared to controls. The increase in SBP was more pronounced in male offspring than in females.

Conclusion: Induced IUGR in rats leads to significantly elevated blood pressure, with a greater effect observed in males. Rat models provide valuable insights into the developmental origins of hypertension, though they may overestimate the effect and not fully replicate the human condition. The endothelin system and sex hormones are implicated in this sexually dimorphic response.

Cite this as: Patridina G, Prasetyorini N (2025) Elevated Blood Pressure in Rat Offspring with Induced Intrauterine Growth Restriction: A Systematic Review. *Asian J Heal Res*. 4 (2): 91–98. doi: 10.55561/ajhr.v4i2.244

INTRODUCTION

Intrauterine growth restriction (IUGR) is a common yet complex problem in obstetrics. IUGR is estimated to affect 10-15% of pregnant women worldwide [1]. Every year, about 13.7 million babies are born underweight [2]. The incidence of IUGR is reported to be six times higher in underdeveloped and developing countries compared to developed nations [2]. IUGR is defined as a deviation from normal fetal growth due to innate growth restriction or adverse environmental factors affecting the fetus's race and gender [3,4]. IUGR plays a significant role in fetal, neonatal, and adult health. Early in pregnancy, fetal growth is primarily driven by cell division (hyperplasia), which later transitions to cell enlargement (hypertrophy) as the primary growth mechanism after hyperplasia stops [3,4].

If fetal development is disrupted during the hyperplastic phase, the size of both the organs and the fetus will decrease. Low birth weight combined with additional problems substantially increases morbidity and mortality throughout the perinatal period [5,6]. IUGR is correlated with various adverse outcomes such as cerebral palsy, growth retardation, short stature, neurodevelopmental impairment, obesity, diabetes, and hypertension, which can manifest in infancy and adulthood. Infants with permanent neurodevelopment impairments experience lower intelligence, poor academic performance, social competence, behavioral issues, motor and psychological disorders, and long-term global cognitive deficiencies [7,8].

Originally, the "early" or "fetal" roots of adult illness theory, which was put forth by Barker et al., suggests that environmental factors, particularly inadequate

nutrition, during early life can program an increased risk for the early development of metabolic disorders and premature mortality in adulthood [9,10].

Pre-eclampsia, a condition linked to IUGR, is associated with reduced uteroplacental perfusion and placental ischemia, which result in a cascade of inflammatory events [6,11]. Placental ischemia is theoretically hypothesized to lead to maternal vascular endothelium dysfunction, vasoconstriction, and hypertension [11]. The three key mechanisms proposed to explain the relationship between placental ischemia and oxidative stress are (1) ischemia-reperfusion and hypoxia, which enhance reactive oxygen species production through mitochondrial pathways or proteolytic cleavage; (2) oxidative stress generated during protein folding; and (3) activation of intracellular inflammatory pathways in response to unfolded proteins [12–14].

Among numerous factors and conditions associated with IUGR, placental insufficiency is the most widely recognized [15]. Placental insufficiency occurs when spiral arteries fail to convert into low-resistance vessels due to uneven blood circulation and ineffective exchange of oxygen and nutrients. This can lead to increased hypoxemia and lactic acidemia, ultimately affecting fetal blood flow and restricting fetal growth. Placental insufficiency also increases free radical production and vascular malfunction, resulting in changes to oxidative metabolism and potential treatment implications [16,17]. Additionally, women with preeclampsia and a history of pregnancy affected by IUGR have a 20% risk of recurrence in future pregnancies [11].

Animal studies have provided valuable insights into the relationship between IUGR and blood pressure (BP). While some studies found no significant impact, others observed elevated BP following IUGR [18,19]. Conducting human studies is challenging due to ethical and methodological limitations. In contrast, animal studies offer the advantage of experimental research, with well-controlled designs and lower variability between subjects, thereby allowing valuable mechanistic insights. Previous meta-analyses on birth weight and blood pressure in humans have been limited by the lack of distinction between preterm birth and IUGR, as well as the inclusion of studies examining a wide range of birth weights [20,21].

To our knowledge, no formal meta-analysis has specifically evaluated the impact of IUGR on blood pressure in either human or animal models. Therefore, this study aims to assess the effects of IUGR induced by placental insufficiency on blood pressure in first-generation rat offspring. Additionally, we seek to identify subgroups that may be predisposed to hypertension following IUGR.

MATERIAL AND METHODS

Data Sources and Search Strategy

On February 10, 2023, a systematic search of PubMed, SpringerLink, and the Cochrane Library was conducted to identify animal studies examining prenatal effects in two groups: (1) IUGR rat offspring models and (2) controls using the PRISMA Guideline [22].

Study Selection

The literature selection process was carried out in two phases. First, titles and abstracts were screened for relevance. Next, full texts of eligible articles were reviewed for final inclusion. In cases of disagreement, a third independent reviewer was consulted to reach a consensus. The selection criteria were (1) conducted on mammals, (2) confirmed and documented restricted birth weight in IUGR offspring, (3) the presence of a normal-growth control group, (4) documented blood pressure (BP) measurements, and (5) no premedication with antihypertensive agents before BP assessment. Studies focusing on nutrient restriction-induced IUGR were excluded, as they do not closely mimic the primary causes of placental insufficiency.

Assessment of Study Quality

Study quality was assessed using SYRCLE's tool for assessing the risk of bias.

Data Extraction

Group-specific data were retrieved, including research design, subject characteristics, birth weight, gestational age, FGR induction techniques for animal studies, and blood pressure readings (MAP, systolic BP, and diastolic BP). In the event of any missing data, the corresponding authors were contacted once via email.

Statistical Analysis

A meta-analysis was conducted using Review Manager 5 to evaluate the effect of reduced uterine perfusion on blood pressure in rat offspring.

RESULTS

The search identified 343 studies, of which 8 met the inclusion criteria. Gestational age follow-up ranged from 3 to 78 weeks, and blood pressure (BP) was measured in the conscious state in all studies. The literature selection process is illustrated in the flowchart (Fig.1), and the assessment of study quality is presented in Table 1. Forest and funnel plots are provided in Fig.2 and Fig.3.

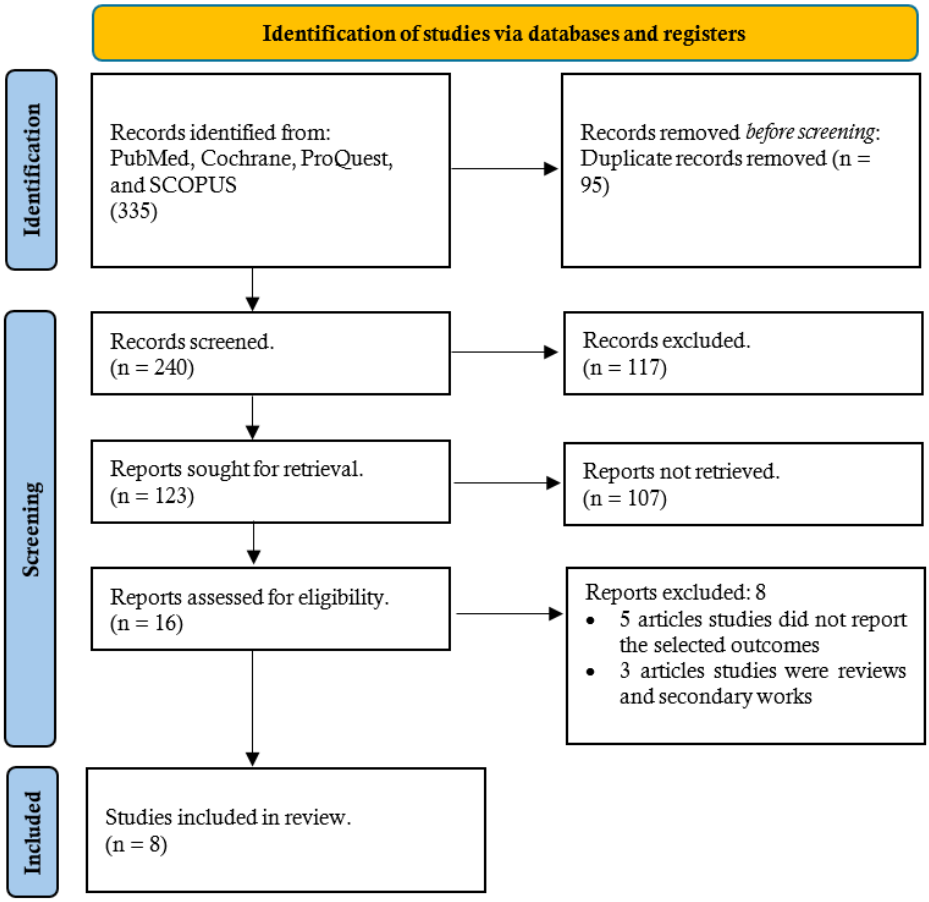


Fig.1. Literature Flowchart

A significant increase was observed in both mean arterial pressure (MAP) (Mean Difference: 9.84, 95% CI: 2.69–16.99, p = 0.007) and systolic blood pressure (SBP) (Mean Difference: 13.09, 95% CI: 7.87–18.32, p < 0.00001) between the experimental and control groups. The increase of SBP in male groups (Mean Difference: 16,54, 95% CI: 11,21-21,87, p<0.00001) was higher compared to female groups (Mean Difference: 11,11, 95% CI: 1,02-21,20, p<0.03). The primary sources of bias in the included studies were related to the randomization of animal subjects and blinding, as these procedures were not explicitly stated in most papers, contributing to a moderate risk of bias. However, all studies adequately controlled for baseline characteristics, and no incomplete data reporting was identified.

DISCUSSION

Reduced uterine perfusion in rats significantly increased blood pressure in both male and female offspring. Hypoxia, resulting from reduced uterine perfusion, has been shown to impair the growth and development of the fetus, increasing the risks of various health problems, including hypertension [23]. The mechanisms underlying this effect remain a subject of debate, with several proposed pathways that include the renin-angiotensin system, oxidative stress, sex hormones, and vascular function alterations [25].

The results of this meta-analysis suggest that the increase in blood pressure due to reduced uterine perfusion differs between male and female offspring. A study by Bourque et al. found that tezosentan, an endothelin receptor antagonist, partially mitigated the blood pressure changes induced by reduced uterine perfusion [25]. Additionally, levels of big endothelin-1 (bET-1), an inactive precursor of endothelin-1 (ET-1), were significantly higher in male offspring, suggesting the role of the endothelin system and pathway in the development of hypertension caused by early prenatal stressors [30,31]. The difference in blood pressure between genders could be influenced by estrogen through the interference of the endothelin system signaling and endothelin release [32,33].

Another study highlighted the role of reduced uterine perfusion, which results in significant hypoleptinemia in offspring. Leptin plays a huge role in regulating energy metabolism, satiety, and promoting optimal fetal growth [34]. The correlation between leptin levels and blood pressure was found to be insignificant, with no significant difference between genders. A moderate positive correlation between leptin levels and body weight suggests the role of maternal hypoleptinemia in altering fetal leptin metabolism, possibly increasing the risk of obesity later in life. In the study done by Tran et al., the difference between male and female offspring's blood pressure was attributed to the difference in measured urinary excretion, which was associated with changes in the nephron and the expression of genes in the renin-angiotensin system, necessitating further research to elucidate the exact mechanisms underlying this change [28].

The restriction of uterine perfusion induces a two-fold increase in male offspring's testosterone levels. Testosterone was shown to induce oxidative stress in male rats, whereas castration causes a reduction in blood pressure [35–37]. Testosterone plays a role in inducing oxidative stress in male hypertensive rats. Catalase, an antioxidant enzyme, is strongly regulated by estrogen, predominantly found in females. Both of these sex hormones affect the dynamics of antioxidant and oxidative stress in vascular function [38–40].

Although this study employed a rigorous methodology, the limited number of included studies constrains the ability to fully predict the impact of hypertension on IUGR.

CONCLUSION

Reduced uterine perfusion in rats significantly elevated blood pressure. Male offspring experienced a larger increase in blood pressure compared to female offspring. The endothelin system and sex hormones appear to contribute to this difference. Further research is needed to identify and understand other causes of blood pressure increase in both genders.

ACKNOWLEDGMENT

The authors would like to express sincere gratitude to all team members for their invaluable support in the completion of this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Table 1. Assessment of Study Quality

Author	Year	Sample	Results
Dasinger et al.[23]	2016	Sprague-Dawley rats exposed to reduced uterine perfusion via surgery at day 14 of gestation or sham procedure	MAP was significantly elevated in growth-restricted offspring compared with control at 12 months of age (P<0.05)
Ojeda et al.[24]	2012	Sprague-Dawley rats exposed to reduced uterine perfusion via surgery at day 14 of gestation or sham procedure	MAP was significantly elevated in male growth-restricted offspring compared with controls at 16 weeks of age (P<0.05), but no significant difference in the female counterpart
Bourque et al.[25]	2013	Sprague-Dawley rats exposed to reduced uterine perfusion via surgery at day 14 of gestation or sham procedure	Systolic BP were elevated in male offspring compared to control at 14 months of age (P<0.01), but no significant difference in the female counterpart
Intapad et al.[26]	2013	Sprague-Dawley rats exposed to reduced uterine perfusion via surgery at day 14 of gestation or sham procedure	MAP was significantly elevated in growth-restricted offspring compared with controls at 12 months of age (P<0.001), but no significant difference at 6 months of age
Master et al.[27]	2014	Wistar-Kyoto rats exposed to reduced uterine perfusion via surgery at day 18 of gestation or sham procedure	Systolic BP was elevated in F1 and F2 offspring compared to control at 6 months of age (P<0.05)
Tran et al.[28]	2015	Wistar-Kyoto rats exposed to reduced uterine perfusion via surgery at day 18 of gestation or sham procedure	Systolic BP was elevated in male offspring compared to controls at 6 and 9 months of age (p<0.05) and in female offspring compared to control at 12 months of age (p<0.05)
Mazzuca et al.[29]	2010	Wistar-Kyoto rats exposed to reduced uterine perfusion via surgery at day 18 of gestation or sham procedure	No statistically significant difference in MAP, systolic, and diastolic BP between groups

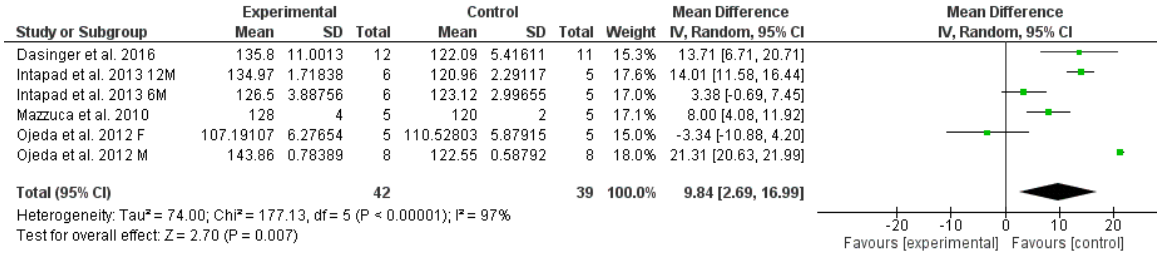


Fig.2. Difference in MAP Measurement between Experimental and Control Groups

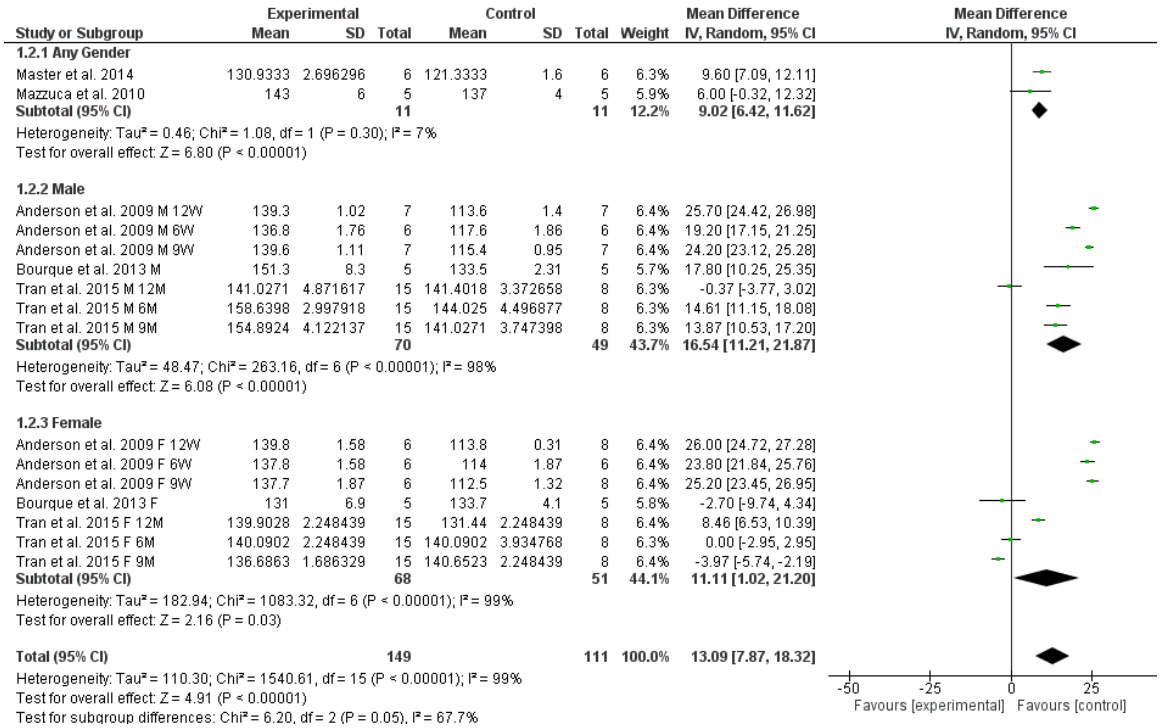


Fig.3. Difference in SBP Measurement between Experimental and Control Groups