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REVIEW ARTICLE

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L-Arginine supplementation in pregnancy: a systematic review of maternal and fetal outcomes

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ABSTRACT

Background/aim of the study: L-Arginine (L-Arg)/Nitric Oxide (NO) system is involved in the pathophysiology of relevant Obstetric conditions. This review aims at summarizing the effects of L-Arg supplementation in pregnancy looking at safety and efficacy.

Methods: We conducted a systematic review of the literature utilizing PubMed for studies published from inception to September 2022. The search included human and animal studies where L-Arg was supplemented pre-conceptionally or during pregnancy, by either oral or intravenous route. The main perinatal outcomes were focused.

Results: Among 1028 publications, 51 studies were eligible for inclusion, 25 were performed in women, and the remnant in animals. Compared to controls/placebo, the supplementation with L-Arg reduced the development of pre-eclampsia (four studies), decreased blood pressure, and reduced the need for antihypertensive drugs in women with Hypertensive Disorders of Pregnancy (HDP, eight studies). In women carrying growth retarded fetuses, L-Arg improved fetoplacental circulation, birth weight and neonatal outcomes (five studies), while in the case of threatened preterm birth, L-Arg reduced uterine contractions (two studies). In several animal species, L-Arg supplementation in pregnancy improved reproductive performance by increasing the litter number and size. Moreover, in pre-eclamptic and metabolic syndrome experimental models, maternal hypertension and fetal growth were improved.

Conclusion: L-Arg displays biological activities in pregnancies complicated by HDP and growth restriction, both in women and animal models. L-Arg administration is safe and could be a candidate as an intervention beneficial to maternal and fetal outcomes, at least in moderate clinical disorders.

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L-Arginine; pregnancy; perinatal outcomes; human studies; animal studies

Introduction

Hypertensive disorders of pregnancy (HDP) remain one of the major causes of pregnancy-related maternal and fetal morbidity and mortality, worldwide. Affected women are also at increased risk for cardiovascular disease later in life, independently from traditional cardiovascular risks [1]. Pre-eclampsia (PE) is the most severe HDP and represents one of the main causes of maternal death [2]. Being the most important reason for iatrogenic prematurity, PE is a major contributor to perinatal mortality and fetal growth restriction [3].

Placental insufficiency (or uteroplacental vascular insufficiency) is another important issue in pregnancy that compromises fetal growth and increases the risks of low birth weight, IUGR, pre-term birth, and stillbirth [4–7].

A recent systematic review and meta-analysis by Goto [8], conducted on human studies, confirmed a pathophysiological role of L-Arg in placental function and vascular compliance, on which pregnancy outcomes may be dependent [5] and reported the favorable effects of prenatal oral l-arginine on birth outcomes.

L-Arg has the potential to improve birth outcomes in pre- and peri-conceptional strategies, being also beneficial for pregnant women, their families, health professionals and policy makers. However, despite arginine being a topic studied by several researchers, there are still many unexplored areas in which it may

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play a role, such as the metabolic profile during pregnancy.

This systematic review aims to summarize the results of main human and animal studies supplementing L-Arginine either orally or intravenously during pregnancy in terms of pregnancy and perinatal outcomes, to finally underline the future research prospective of this semi-essential amino acid.

Materials and methods

Literature search and data extraction

This systematic review followed the PRISMA guidelines [9].

A comprehensive literature search was conducted in PubMed (www.ncbi.nlm.nih.gov) for studies published from inception to September 2022, using as keywords: L-Arginine OR Arginine OR Nitric Oxide donor OR Arginine supplementation AND preeclampsia OR high-risk pregnancy OR fetal growth restriction OR hypertension OR hypertension in pregnancy OR perinatal outcomes). In addition to database searches, we performed a full-text review of studies included in meta-analyses investigating the effects of L-Arg supplementation in high-risk pregnancies on perinatal outcomes, selecting 4 more trials from two metanalysis [8,10].

This systematic review included both human and animal studies. We restricted our search to studies published in English. Review articles were excluded after a search of the reference lists.

Study selection

After the primary records were retrieved from PubMed, duplicates were removed. The remaining records' titles and abstracts were screened, and irrelevant studies were excluded. Full texts of studies deemed relevant were obtained and reviewed in detail for eligibility according to the inclusion criteria. Reviews, Letters to the Editor, meeting précis and other articles reporting studies that did not provide the primary data were excluded.

Publications were included in the final analysis if they met the following inclusion criteria: studies evaluating supplementation of L-Arg during pregnancy or it the pre-gestational and postnatal period. Studies with unclear treatment details or with a combination of several amino acids/supplements were excluded. At least one of the following outcomes was used as a primary or secondary endpoint: maternal hypertension, pre-eclampsia, fetal growth restriction/retardation, feto/placental hemodynamic, birthweight, perinatal outcomes. In case of human treatment, only randomized controlled trials and prospective or retrospective cohort studies were considered.

Studies were excluded according to the following criteria: narrative reviews, systematic reviews and meta-analyses, studies evaluating pathophysiology rather than clinical outcomes, studies published in other languages than English.

Analysis

The outcomes evaluated included maternal hypertensive disorders, pre-eclampsia, fetal growth restriction/-retardation, and perinatal outcomes. We defined maternal hypertensive disorders as blood pressure values above 140/85 mmHg, pre-eclampsia as elevated blood pressure associated with proteinuria and/or the presence of kidney or liver function alterations, neurological signs, hemolysis or thrombocytopenia and/or fetal underdevelopment [11].

Fetal growth restriction as an estimated fetal weight $<$10th percentile [12], while perinatal outcomes included birthweight, Apgar score, delivery mode, NICU admission.

We also explored the association between maternal blood pressure levels during pregnancy and offspring outcomes whenever it was possible.

Results

Flow chart

The literature search identified 1028 articles, of which 21 duplicate records were removed. The remaining 1007 records were screened and 75 of them matched the inclusion criteria. These studies were then assessed for eligibility: five narrative reviews, 10 systematic reviews and meta-analyses, two studies with unclear treatment strategies, three studies evaluating the pathophysiologic basis of disease, and four studies with unavailable full text were excluded. Thus, our review was restricted to 51 studies (Figure 1).

Human studies

Doses and timing of administration

Among the 25 human studies, L-Arg was administered orally in 16, intravenously in eight, and a mixed treatment was done in the remnant as reported in Table 1. Oral treatment doses ranged from 1 g/day [13] to 16 g/day [14, 15], lasting from 8 to 10 days [15] to the entire duration of pregnancy [16]. Intravenous administrations were mainly utilized in the acute treatment

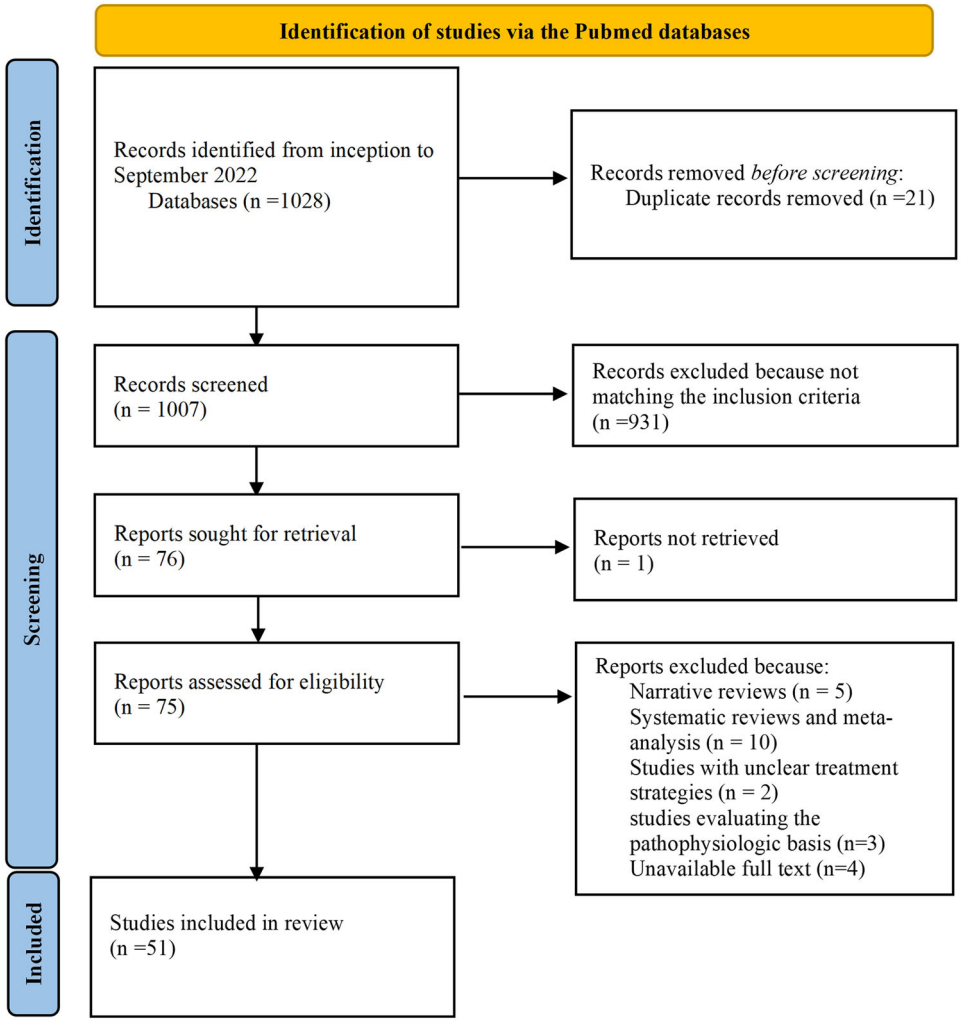

Figure 1. Flow diagram of the study selection.

of hypertension, PE or severe IUGR, doses ranging 15 g (in 500 ml of 5% glucose) [17] to 30 g (in 100 ml of saline) [18]. Treatments usually lasted one day, except for the study by Xiao et al. [19] which administered L-Arg for 7 days to women carrying IUGR fetuses.

L-Arginine and assisted reproductive technology

L-Arg was administered in three studies to women undergoing assisted reproductive technology (ART) [14, 15, 20]; medications were taken orally in addition to gonadotrophin-releasing hormone analogue (GnRHa) and pure follicle stimulating hormone (pFSH) [14, 15], or in addition to folate and vitamin E [20]. L-Arg led to less cycle cancelation, more oocytes and transferred embryos, increased plasma and follicular fluid nitrite/nitrate, as well as to Doppler flow improvement in one study [15]. A detrimental role of L-Arg was reported on embryo quality and pregnancy rate during controlled ovarian hyperstimulation cycles, due to the inverse correlation between follicular fluid concentration of nitrite/nitrate and embryo quality [14]. On the contrary, So [20] reported that, especially in cases of male infertility, both biochemical and clinical pregnancy rate were significantly increased by L-Arg (Table 2).

L-Arginine supplementation and fetal growth restriction

L-Arg was administered in seven studies to women carrying IUGR fetuses: in three of them the administration occurred intravenously while in the remnant 4 it was oral. Overall, the studies showed that L-Arg infusion affects utero-placental circulation by lowering the uterine artery pulsatility index [18], improving birthweight [19, 21, 22], reducing placental apoptosis, and improved placental function and fetal development [17]. L-Arg also reduced the incidence of abnormal umbilical artery blood flow and uterine artery early—diastolic notching [23], being not effective for severe vascular IUGR in possibly due to the severity of the

Table 1. Main human study characteristics.

Author	Year	Study design	Population	N	Administration	Intervention	Duration of treatment
Battaglia C et al.	1999	RCT	ART	17/17	Oral	GnRHa + pFSH GnRHa + pFSH + 16 g L-Arg/day	8–10 days
Battaglia C et al.	2002	RCT	ART	18/19	Oral	GnRHa + pFSH + 16 g L-Arg GnRHa + pFSH + placebo	8–10 days
So S et al.	2020	RCT	ART	36/37/36	Oral	AS2000 group, L-Arg, 2 g + folate 400 μg + vitamin E 10 mg; AS1000 group L-Arg 1 g + folate 200 μg	Maximum 3 months
Neri I et al.	1996	RCT	IUGR	9/9/9	Intravenous	L-Arg infusion for 30 min (30 g/100 ml)	1 day
Sieroszewski P et al.	2004	Clinical trial	IUGR	78/30	Oral	L-Arg 3 g /day for 20 days	20 days
Xiao XM et al.	2005	Clinical trial	IUGR	30/36/30	Intravenous	20 g/day of L-Arg/routine therapy/control	7 days
Shen SF et al.	2011	RCT	IUGR	30/30	Intravenous	15 g of L-Arg in 500 ml 5% glucose, daily /control	1 day
Singh S et al.	2015	Clinical trial	IUGR	60/30/30	Oral	L-Arg 3 g daily for 21 days	21 days
Ropacka M et al.	2007	RCT	HDP and IUGR	124/78	Oral	L-Arg 3 g daily/placebo	Until delivery
Winer N et al.	2009	RCT	severe IUGR	21/22	Oral	14 g/day of L-Arg/placebo	Until delivery
Staff AC et al.	2004	RCT	PE	15/15	Oral	4 g of L-Arg/placebo	2 days
Neri I et al.	2004	RCT	HDP	7/7	Intravenous	Infusion of L-Arg 20 g/500 ml/placebo	1 day
Rytlewski K et al.	2005	Clinical trial	PE	30/31	Oral	3 g L-Arg/routine therapy/control	1–4 weeks after PE diagnosis and continued until 36 weeks of pregnancy
Neri I et al.	2006	RCT	HDP	80/80	Intravenous	L-Arg (20 g/500 ml) or placebo IV	5 days
Rytlewski K et al.	2006	RCT	PE	30/31	Oral	3 g L-Arg/routine therapy/control	3 weeks
Hladunewich MA et al.	2006	RCT	PE	22/23	Oral or intravenous	L-Arg orally (3.5 g every 6 h), or intravenously (10 g every 8h) when medications could not be taken orally	Median of 6 days before delivery (range 3–17)
Facchinetti F et al.	2007	RCT	HDP	40/40	Intravenous	L-Arg (20 g/500 ml intravenously daily, for 5 days followed by 4 g/day orally for 2 weeks) or placebo	5 days
Valdivia-Silva JE et al.	2009	RCT	PE	50/46	Oral	L-Arg 1 g 3 times a day	3 weeks
Neri I et al.	2010	RCT	CH	40/40	Oral	L-Arg 4 g/day /placebo	10–12 weeks
Monari F et al.	2021	RCT	CH and previous placenta vascular disorders	30/49	Oral	L-Arg 3 g (+Mg 350 mg and Sal extract 100 mg) + LDA 100 mg/day *vs.* only LDA 100 mg/day	Entire pregnancy
Vadillo-Ortega F et al.	2011	RCT	PE high risk population	228 222 222	Oral	6.6 g of L-Arg + antioxidant vitamins/placebo	Until delivery
Camarena Pulido EE et al.	2016	RCT	high risk pregnancies	50/50	Oral	3 g of L-Arg a day/placebo	From 20 to 39 weeks
Rytlewski K et al.	2008	RCT	threatened PTB	30/31	Oral	3 g of L-Arg/placebo	Since 1–4 weeks after admission to hospital until delivery
Facchinetti F et al.	1996	Clinical trial	threatened PTB	10	Intravenous	L-Arg was infused for 30 min 30 g/100 ml	1 day
Petrella E et al.	2014	Clinical trial	Overweight/obese	10/12	Intravenous	L-Arg (20 g/500 ml in 3h)	1 day

Table 2. Main findings of human studies.

Author	Year	Population	Main outcome	Main finding
Battaglia C et al.	1990	ART	Uterine and follicular Doppler flow and ovarian response to gonadotrophin in poor responder women	Lower cancelation rate, increased oocytes collected, and transferred embryos, increased plasma, and follicular fluid concentrations of arginine, citrulline, NO_2^-/NO_3^-, and IGF-1. Significant Doppler flow improvement in the L-Arg-supplemented group
Battaglia C et al.	2002	ART	Hormonal, ultrasonographic and Doppler evaluations, and plasma and follicular fluid nitrite/nitrate concentrations	L-Arg may be detrimental to embryo quality and pregnancy rate during controlled ovarian hyperstimulation cycles
So S et al.	2020	ART	hCG-positive rate or CPR in 3 months	Higher hCG-positive rate and CPR in L-Arg group. In the subgroup of male infertility, the hCG-positive rate and CPR were significantly increased by L-Arg
Neri I et al.	1996	IUGR	Utero-placental circulation	L-Arg infusion affects utero-placental circulation in patients with IUGR associated with increased uterine resistances
Sieroszewski P et al.	2004	IUGR	US estimated weight	L-Arg improved the estimated fetal weight and birthweight
Xiao et al.	2005	IUGR	Birtweight and maternal NO serum levels	L-Arg increased maternal NO_2^-/NO_3^- levels and mean birthweight
Shen SF et al.	2011	IUGR	Parameters of fetal growth and development monitored by B-ultrasound at regular intervals	L-Arg reduced the expression of Bax, and enhanced the expression of bcl-2, associated with reduced placental apoptosis, and improved placental function and fetal development
Singh S et al.	2015	IUGR	Birthweight and maternal NO serum levels	L-Arg can be used to increase maternal NO levels, enhancing birthweight, and decreasing neonatal morbidity
Ropacka M et al.	2007	HDP and IUGR	Feto-maternal hemodynamic	L-Arg reduced incidence of abnormal umbilical artery blood flow and uterine artery early—diastolic notching
Winer N et al.	2009	severe IUGR	Birth weight and neonatal morbidity	L-Arg is not effective for severe vascular IUGR
Staff AC et al.	2004	PE	Diastolic blood pressure	Oral L-Arg supplementation did not reduce mean diastolic blood pressure after 2 days of treatment compared with placebo in pre-eclamptic patients with gestational length varying from 28 to 36 weeks
Neri et I al.	2004	HDP	Fetal heart variables by a computerized non-stress test (NST)	L-Arg infusion did not affect cardiac variables and fetal movements but showed an acute hypotensive effect of systolic and diastolic values
Rytlewski K et al.	2005	PE	SBP, DBP, MAP	L-Arg significantly lowered SBP, DPB, and MAP and elevated 24-h urinary excretion of NOx and mean plasma levels of l-citrulline. Exogenous L-Arg did not influence plasma concentrations of L-Arg, L-ornithine and methylated arginines
Neri I et al.	2006	HDP	Systolic and diastolic blood pressure	L-Arg showed an anti-hypertensive role, both SBP and DBP were reduced
Rytlewski K et al.	2006	PE	Fetal condition and neonatal outcome	L-Arg improved fetal well-being and neonatal outcome and prolonged pregnancy complicated with PE
Hladunewich MA et al.	2006	PE	MAP, glomerular filtration rate, proteinuria assessed on 3rd and 10th days postpartum by inulin clearance and albumin:creatinine ratio	L-Arg improve markedly blood pressure and kidney function the 10th day postpartum without hasten the recovery
Facchinetti et al.	2007	HDP	Time from randomization to delivery (Latency)	L-Arg seems promising in prolonging pregnancy and reducing blood pressure
Valdivia-Silva JE et al.	2009	PE	Fetal growth retardation	L-Arg markedly improved fetal growth
Neri et al.	2010	CH	BP change after 10-12 weeks of treatment and percentage of women on antihypertensive treatment at delivery, maternal, and fetal outcome	BP did not change after 10–12 weeks of treatment. Lower % of women received antihypertensive drugs in the L-Arg group. The incidence of superimposed PE indicated delivery before the 34th weeks and certain neonatal complications tended to be higher in the placebo group
Monari et al.	2021	CH and previous placenta vascular disorders	Improvements of perinatal outcomes in LDA + L-Arg group, considering	Promising results on BP values, uterine artery PI and the lower need to start a new antihypertensive treatment
Vadillo-Ortega et al.	2011	PE high-risk population	PE	Reduced the incidence of PE
Camarena Pulido et al.	2016	PE high-risk pregnancies	The resulting impact in reducing pregnancy medicalization	L-Arg reduced the cases of PE and led to higher birthweight and less PTB
Rytlewski et al.	2008	threatened PTB	Feto-placental circulation in women with threatened preterm labor.	Oral supplementation with low doses of L-Arg changed feto-placental blood flow distribution in patients with threatened preterm labor
Facchinetti et al.	1996	threatened PTB	Spontaneous uterine contractility	L-Arg significantly reduced the number of contractions, together with an increase of both serum growth hormone and nitrates levels
Petrella et al.	2014	Overweight/obese	Insulin signaling and endothelial function	In overweight/obese women, no responses to L-Arg were found in the 1st or 2nd trimesters. In the 1st trimester, insulin levels were significantly reduced in both groups after L-Arg infusion. Insulin levels during weeks 24–27 were suppressed only in normal-weight women after L-Arg infusion

growth retardation (3rd percentile) and to the early course of gestation (28 weeks) [24] (Table 2).

L-Arginine and hypertensive disorders of pregnancy

In 11 studies L-Arg was used to treat women with hypertensive disorders of pregnancy (HDP), chronic hypertension (CH), or preeclampsia (PE). Three studies administered L-Arg intravenously while seven orally and one either orally or intravenously when oral medication could not be taken [25].

Five studies included women diagnosed with PE [25–29], and treatments lasted from 2 days (acute treatment) [27] to 3 weeks [29]. L-Arg supplementation lowered systolic blood pressure (SBP), diastolic blood pressure (DPB), mean arterial pressure (MAP) and increased 24-h urinary excretion of NOx as well as plasma levels of L-citrulline [26]. Moreover, L-Arg markedly improved fetal growth [29] fetal well-being, neonatal outcome and prolonged pregnancy [28]. L-Arg also significantly improved blood pressure and kidney function the 10th day postpartum without hasten the recovery of women with PE [25]. An acute treatment of PE patients with gestational length varying from 28 to 36 weeks (4 g of L-Arg for 2 days orally) with L-Arg supplementation did not reduce mean diastolic blood pressure compared with placebo (Staff AC).

Three studies were conducted on women with HDP [30–32] and L-Arg was administered intravenously (20 g/day, for a maximum of 5 days). L-Arg infusion showed an acute hypotensive effect both on systolic and diastolic values [30, 31], without affecting fetal movements, while prolonging pregnancy [31].

The remnant studies included women at high risk for PE [33, 34] or suffering CH [16, 35]. Oral prophylactic treatments started in the first trimester and lasted from 10 weeks to the entire duration of pregnancy (more than 30 weeks). Although L-Arg did not change BP a lower percentage of women required antihypertensive drugs [35] and improved uterine artery impedance [16]. PE was lesser developed and the incidence of superimposed PE indicating early delivery $<$34 weeks show a trend to be reduced [33–35]. L-Arg treatment was also associated with higher birthweight and less preterm births [34].

Two studies were conducted in women with threatened preterm birth (PTB), one using 3 g/day of orally since admission until delivery [28], while the other acutely infusing L-20 g/500 ml in 3 h of L-Arg [36]. Oral supplementation increased feto-placental blood flow while i.v. infusion reduced uterine contractions, increasing both serum growth hormone and nitrates levels.

Transgenerational/metabolic effects of L-Arg

A single study evaluated L-Arg/NO system and its role in insulin signaling and endothelial function in pregnant women of different BMI categories [37]. NO availability was found impaired in overweight/obese women, and this deranged endothelial function and insulin regulation. L-Arg reduced insulin level in the first trimester, only in normal-weight in the second trimester.

Animal studies

Doses and timing of administration

In 23 out of 26 animal studies, L-Arg was administered orally, either dissolved in drinking water or introduced with the diet, whereas in the remnant 3 studies it was administered intravenously [38–40] (Table 3).

Studies focused on the effects of L-Arg on reproductive performances (five studies), fetal growth (16 studies), hyperinsulinemia and/or hypertensive disorders (four studies) while immune response was outcome of the remnant study.

L-Arginine and reproductive performance

Pigs [41–43], mares [44], and ewes [38], were the target of L-Arg. In mares L-Arg reduced uterine fluid accumulation, without altering follicular development, representing a breeding management tool in postpartum period to increase reproductive success [44]. Moreover, L-Arg markedly increased live-born piglets by two per litter [41] and increased birthweight [43], also improving lactation performance of first-parity sows [42]. No effects were found in lambing rates [38] (Table 4).

L-Arginine supplementation and fetal growth

Supplementation (mainly *via* drinking water or through diet) was done in undernourished sheep (six studies), pigs (eight studies), rats (two studies).

Generally, L-Arg increased birth weight and muscle weight as well as maturation [39, 45, 46] possibly through altered mTOR protein abundance [39]. No effect on the stillbirth rates was found in sows [47], while L-Arg supplementation enhanced fetal survival [48, 49] in swine. In sheep L-Arg (and NCG) supplementation decreased IUGR by improving metabolic homeostasis and through the expression of fetal somatotropic axis genes [50, 51]. Zhang et al. 2016 [52] confirmed the promotion of fetal-placental

Table 3. Main characteristics of basic science studies.

Author	Year	Animal model	Indication/target	Administration	Intervention
Kelley D et al.	2013	Multiparous Quarter horse mares	Reproductive parameters	Oral	100 g L-Arg for 1 day during the last 3 weeks of pregnancy
Mateo et al.	2007	52 pregnant gilts (Camborough 22, Pig Improvement)	Reproductive performance	Oral	Corn-soybean-based diets supplemented with 1.0% L-Arg-HCl or 1.7% L-alanine
Mateo et al.	2008	38 first-parity sows (Camborough 22, Pig Improvement Co., Franklyn)	Lactation performance	Oral	1% L-Arg-HCl or 1.7% L-Ala
Li et al.	2015	Exp 1. 62 Landrace gilts (Parity 1) and 113 sows Exp 2. 155 multiparous Landrace sows (Parity $\geq$ 2)	Reproductive performance	Oral	Exp 1. corn- and soybean meal-based diet supplemented with 1.3% L-Arg HCl or 2.2% l-alanine. Exp 2. 1.3% L-Arg HCl supplementation between d 1 and 14 ($n = 41$), d 15 and 30 ($n = 40$), or d 1 and 30 ($n = 37$), control group 2.2% l-alanine supplementation between d 1 and 30 ($n = 37$).
Crane et al.	2016	Multiparous Rambouillet ewes naturally stimulated	Reproductive parameter	Intravenous	Injectable and oral Arg supplementation provided for 14 d post breeding
Sales F et al.	2016	Multiparous Romney ewes, with a diet supplement	Fetal growth	Intravenous	Intravenous bolus of either 345 μmol Arg HCl/kg BW or saline solution 3/day from day 100 to 140 of pregnancy
de Boo HA et al.	2005	Pregnant Romney ewes undergone placental embolization with Microspheres	Fetal growth restriction	Intravenous	L-Arg or mixed amino acid (AA) infusion
Vosatka et al.	1998	Wistar rats with or without exposure to maternal hypobaric hypoxia	Fetal growth restriction	Oral	0.2% L-Arg, 2% L-Arg, or 2% glycine in drinking water
Sun et al.	2018	Pregnant sheep with nutrient-restriction (fed 50% NRC requirements)	Fetal growth restriction	Oral	10 g/day of rumen-protected arginine and 2.5 g/day of N-carbamylglutamate
Sun et al.	2017	Pregnant sheep with nutrient-restriction (fed 50% NRC requirements)	Fetal growth restriction	Oral	20 g/day rumen-protected arginine or 5 g/day N-carbamylglutamate
Garbossa et al.	2015	Sows receiving dietary supplement	Fetal development	Oral	Control diet, control + 1% Arg, control + 20mg/kg ractopamine (Rac), and control diet + Arg + Rac from day 25 to 53 of gestation
Berard et al.	2010	Swiss Large White gilts with dietary supplement	Fetal development and myogenesis	Oral	26 g of L-Arg daily from 14 to 28 days of gestation/control
Quensel et al.	2014	Highly prolific crossbred Landrace × Large White sows under 3 dietary supplements	Fetal growth	Oral	Dextrose the week before insemination (190 g/d) and of L-Arg (25.5 g/d) from d 77 of pregnancy until term (DEXA, $n = 26$); a dietary supplementation of L-Arg only (25.5 g/d), from d 77 of pregnancy until term (ARGI, $n = 24$)
Gao et al.	2012	Gestating pigs (Yorkshire × Landrace, $n = 108$) with dietary supplement	Fetal and placental growth	Oral	1.0% L-Arg HCl or 1.7% L-alanine
Li et al.	2010	Gilts (F1 crosses of Yorkshire 3 Landrace sows and Duroc 3 Hampshire boars) with dietary supplement	Fetal growth	Oral	0.0, 0.4, or 0.8% L-Arg (wt:wt) between d 0 and 25 of gestation (10 gilts/treatment)
Li et al.	2014	Gilts (F1 crosses of Yorkshire 3 Landrace sows and Duroc 3 Hampshire boars) with dietary supplement	Fetal growth	Oral	Fed 2/daily 1 kg of a corn- and soybean meal-based diet supplemented with 0.0, 0.4, or 0.8% L-Arg
Bass et al.	2017	97 Pregnant gilts and sows with dietary supplement	Fetal growth and lactation	Oral	Exp 1. control diet 19.8 g standardized ileal digestible Arg/d) or the CON + 1.0% L-Arg (ARG; 46.6 g SID Arg/d). Exp 2. CON or ARG, Sows received 2.73 kg feed/d with CON sows provided 17 g SID Arg/d and ARG sows for a total of 44 g SID Arg/d.
Madsen et al.	2017	30 Low birthweight piglets with dietary supplement	Growth performance	Oral	Milk replacer diets containing either no supplement (CON), CAR (0.40 g/piglet per day) or ARG (1.08 g/kg BW per day)
Zhang et al.	2016	48 Multiparous nutrient-restricted pregnant Hu sheep with dietary supplements	Nutrient restriction	Oral	N-carbamylglutamate (NCG) and rumen-protected L-Arg (RP-Arg)
Peine et al.	2018	32 Rambouillet ewes allocated to 60% restricted diet	Nutrient restriction	Oral	180 mg L-Arg/kg BW (based on initial BW)
Helmbrecht et al.	1996	Timed-pregnant Sprague-Dawley rats receiving L-NAME and dietary supplements	PE, IUGR	Oral	L-Arg (21 mg/kg per day) through delivery
Bursztyn et al.	2003	Pregnant rats with insulin-induced hypertension receiving dietary supplements	Hypertension	Oral	L-Arg given orally (in drinking water) at a dose of 2 g/L
Sharkey et al.	2001	SHHF/Mcc-fa^{cp} (spontaneous hypertension and heart failure) rats receiving dietary supplements	Placenta gene expression, Hypertension, IUGR	Oral	L-Arg in drinking water (0.5 mg/mL)
Altun et al.	2008	Stress-induced preeclamptic pregnant rats with dietary supplements	PE	Oral	21 mg kg^{-1}day^{-1} L-Arg administered *via* orogastric route on the 18th and 19th days of pregnancy
Podjarny et al.	2001	Pregnant rats with insulin-induced hypertension with dietary supplements	Hypertension	Oral	2 g/L of L-Arg in the drinking water from day 11 of gestation until delivery
De Costa et al.	2014	*Trypanosoma cruzi* infected and pregnant Wistar rats with dietary supplements	Chagas disease	Oral	21 mg of L-Arg/kg body weight/day, diluted with distilled water. From this solution, 0.1 ml was given from the 4th day of pregnancy until the 18th day, once a day, in the morning until the day of the experiment

Table 4. Main findings of the basic science studies.

Author	Year	Main outcome	Main finding
Kelley et al.	2013	Plasma Arg concentrations, follicular dynamics, and ovarian and uterine artery blood flow after foaling	Reduced uterine fluid accumulation, while not altering follicular development. L-arg supplementation can be a breeding management tool during the postpartum period to increase reproductive success
Mateo et al.	2008	Reproductive performance of pregnant gilts	L-Arg determined a marked increase of live-born piglets by 2 per litter in gilts
Mateo et al.	2007	Lactation performance of 38 first-parity sows	Potential beneficial effects of dietary Arg supplementation in improving lactation performance of first-parity sows
Li et al.	2015	Reproductive performance of gilts and sows	Dietary Arg supplementation during early gestation increased the number of piglets born alive and live litter birth weight
Crane et al.	2016	Reproductive performance	Supplemental Arg during the first 14 days of pregnancy was ineffective on lambing rates while infusion positively impacted weaning rates
Sales F et al.	2016	Fetal skeletal muscle growth, the abundance and activation of mTOR protein, and postnatal muscle growth of the offspring	Arg increases female lamb weight and muscle weight after birth: changes are associated with altered mTOR protein abundance
de Boo HA et al.	2005	Protein metabolism	Amino acid infusion increased protein accretion better than Arg alone
Vosatka et al.	1998	Fetal growth and hypoxia-induced uricemia	L-Arg ameliorates maternal hypoxia-induced fetal growth restriction in rats
Sun et al.	2018	Fetal growth	Arg and NCG supplementation decreases fetal IUGR by improving metabolic homeostasis and affecting expression of fetal somatotropic axis genes.
Sun et al.	2017	Effects during gestation	The beneficial effect of dietary Arg and NCG supplementation on mammalian reproduction is associated with complex metabolic networks.
Garbossa et al.	2015	Fetal muscle development performance and carcass characteristics of the progeny	L-Arg increased the size of muscular fiber in the semitendinosus muscle of piglets originating from sows. The combination of ractopamine and Arg did not have additive effect and increased the stillbirth
Berard et al.	2010	Porcine fetal development and myogenesis	L-Arginine supplemented during early gestation enhanced fetal survival
Quensel et al.	2014	Within-litter variation of piglet birth weight (BW0)	L-Arg during the last third of pregnancy reduced within-litter changes of birthweight
Gao et al.	2012	Pregnancy outcomes	Dietary Arg supplementation enhances placental growth and estrogen levels in the maternal circulation
Li et al.	2010	Embryonic/fetal survival and growth in gilts	Dietary supplementation with 0.8% L-arginine between day 0 and 25 of gestation, while increasing placental vascularity, adversely affects the reproductive performance of gilts
Li et al.	2014	Embryonic growth and survival	Dietary supplementation with L-Arg at 14–25 days of gestation enhances embryonic/fetal survival in swine
Bass et al.	2017	Piglet birth weight and preweaning performance	Late pregnancy supplementation with L-Arg had no effect on number of pigs born alive, piglet birth weight, or lactation performance
Madsen et al.	2017	Growth performance, carcass composition, organ, and Semitendinosus muscle (STM) development	ARG and CAR supplements were beneficial for muscle maturation
Zhang et al.	2016	Maternal endocrine status; maternal, fetal, and placental antioxidation capability; and placental development	Dietary supplementation of NCG and Arg influence maternal endocrine status, improve the maternal–fetal–placental antioxidation capability, and promote fetal and placental development
Peine et al.	2018	Postnatal growth and development	Arg supplementation during the last two-thirds of gestation can mitigate offspring, but not maternal negative consequences associated with restricted maternal nutrition
Helmbrecht et al.	1996	PE, IURG, and renal glomerular capillary endothelial lesions	L-Arg significantly lowered systolic blood pressure at late pregnancy, increased birthweight, decreased the degree of proteinuria and decreased the proportion of injured glomeruli.
Bursztyn et al.	2003	Endothelial NO synthase in kidney	L-Arg treatment significantly reduced blood pressure, serum creatinine, and excretion of NO metabolites. Expression of endothelial NO synthase in kidneys was doubled
Sharkey et al.	2001	Hypertension and feto/placenta weight	L-Arg prevented the elevation of Blood Pressure, particularly during the third trimester; avoid placenta overweight without effect of fetal growth
Altun et al.	2008	Effect of oral L-Arg treatment on stress-induced hypertensive rats	L-Arg supplementation decreased hypertension, proteinuria and ADMA levels
Podjarny et al.	2001	Fetal growth and blood pressure	L-Arg reversed insulin-induced hypertension and improved fetal weight not affecting plasma insulin/glucose
De Costa et al.	2014	Parasitemia, corticosterone levels, NO production, fetal morphological measurements, heart, and placenta histology	L-Arg supplementation decreased corticosterone and parasitemia, enhanced nitrite concentrations, fetal weight, length and placental weight. Cardiac tissue showed reduced amastigote burdens in the L-Arg group. The placental parasitism was similar between groups

development through the improvement of antioxidation capability.

Placental growth and vascularity were enhanced by L-Arg [53] also in pigs, although Li et al. [54] reported a decreased litter size in gilts.

Once supplemented late in pregnancy, L-Arg had no effect on piglet birth weight or lactation performance [55], being unable to mitigate consequences of restricted maternal nutrition [56] (Table 4).

L-Arg supplementation and hyperinsulinemia/hypertensive disorders

Three studies were conducted on murine models of chronic exogenous hyperinsulinemia, leading to hypertension and heart failure [57–59]. Another study used L-NAME in rats creating a model of preeclampsia [60].

L-Arg reversed the endothelial lesion due to the L-NAME exposure, and lowered blood pressure in late pregnancy [60], decreased the degree of proteinuria and the proportion of injured [58, 60, 61].

The supplementation with L-Arg increased birthweight, without any changes in the levels of plasma insulin or serum glucose [59, 60], but stimulating NO system in the placenta [58] (Table 4).

These data, obtained in different experiment models of insulin-induced rat hypertension, suggest a direct reversal effect of L-Arg administration on hypertension and fetal weight changes, activating NO systems in placenta and kidney.

Immune response and L-Arginine

In *Trypanosoma cruzi* infected pregnant Wistar rats, which allowed Chagas disease development [62], L-Arg decreased the levels of corticosterone and parasitemia and increased fetal and placental weigh, and reduced amastigote burdens. L-Arg supplementation might improve the host immune response during the acute phase (Table 4).

Safety and tolerability of dietary supplementation of L-Arginine

None of the human studies reported adverse events associated with the supplementation with L-Arg during pregnancy, neither for a long period of administration (3 months) [20] nor by using high doses as for the acute treatments (20 or 30 g/100 ml of saline for 1 day or 1 week) [18, 19]. Among animal studies, only one study conducted on sows reported an increase in stillbirth rates, in the group receiving the combination of Arg and Ractopamine (Rac) from day 25 to 53 of gestation [47] (Table 4). However, it is unknown to which supplement such effect could be ascribed.

Discussion

This systematic review of the literature found human and animal studies over a large period of time, witnessing the still actual interest toward L-Arg administration for reproductive purposes.

Overall, the results demonstrated that L-Arg supplementation during pregnancy could be beneficial in several circumstances, especially on maternal hypertension and fetal growth, by reducing blood pressure levels, the onset of preeclampsia, and improving vascularity as well as placental function. However, it is worth emphasizing that many of the RCTs included were conducted more than 15 years ago and had weak power and a heterogeneous population. Also, no data are available on severest outcomes (i.e. stillbirth, placental abruption or severe IUGR), unlike other studies with NO donors [63, 64] which however failed in demonstrating efficacy on the development of FGR, preterm delivery, and perinatal mortality and morbidity.

While pharmacological NO donors have been associated with poor efficacy (Cochrane), L-Arg which is the physiological substrate of endothelial NO synthase seems to show a better risk/benefit profile. Possibly, the production of peroxynitrites as a result of an excess NO bioavailability does not occur when administering the amino acid [65].

However, short-term supplementation of L-Arg, especially late in pregnancy, resulted insufficient to improve maternal hemodynamics and did not mitigate the effects of severe IUGRs [25]. This suggests that L-Arg should be initiated early and continued over the course of the entire pregnancy in order to positively affect blood pressure or placental vascular insufficiency, *via* the arginine–NO pathway [66].

These findings confirm what has been reported in a recent meta-analysis by Goto [8] (based upon solely 10 eligible articles) which concluded that the supplementation with L-Arg should be recommended in women with a history of poor pregnancy outcomes, both in those at high-risk of pre-eclampsia, as well as in those with already established HDP. However, we agree with the authors stating that more trials are required to provide stronger conclusions, since the small study effects.

The partial efficacy of L-Arg may be related to the splanchnic extraction and metabolism of arginine which often precluded its efficacy with possible degradation by arginase. Indeed, animal studies supplementing citrulline (direct NO donor without splanchnic degradation), reported an enhanced placental function and fetal growth in rat models of IUGR through the involvement of insulin-like growth factor 2 and

angiogenic factors [67] and improved perinatal and postpartum maternal vascular function in a mouse model of preeclampsia [68]. Citrulline effectively raised fetal arginine availability, although it failed to increase the concentrations of essential amino acids in fetal plasma of murine models of IUGR [69]. Unfortunately, no human trials are available about Citrulline and/or combined supplementation.

Another systematic review [70] analyzed the role of Arginine synthesis and metabolism in pregnancy and provided evidence for the link between an impaired arginine metabolic pathway and the pathogenesis of compromised pregnancy and fetal programming. Interestingly, the Authors presented L-Arg supplementation as a potential reprogramming strategy during pregnancy, in order to prevent non-communicable diseases (NCDs) in the offspring. Many of the evidence supporting such an idea stay on the capacity of improving fetal growth, also in cases where placenta function is compromised. Accordingly, it has to be remembered that the Barker's observation correlating low than normal weight at birth with the later adult development of cardiovascular diseases was the milestone of epigenetic hypotheses [71].

The fetal somatotrophic stimulation by L-Arg is evident also in several animal species through the exploitation of the amino acid as a booster of NO availability in the placenta vasculature. In addition, we understand from rats that L-Arg display its effects also in cases where hypertension and growth restriction are sustained by chronic hyperinsulinemia allowing insulin resistance [57–59]. Indeed, besides cardiovascular benefits, serum glucose and free fatty acids concentration was reduced in overweight/obese females in fertile period [72] and type 2 diabetes [73]. Although reported only in a single study, the ability of L-Arg to activate endothelium-dependent vasodilation in obese pregnant women reducing circulating insulin levels suggests the possible employment of supplementation in such a condition, well characterized as being insulin-resistant [37]. Interestingly, among possible target of L-Arg administration there are also women with a reduced pre-pregnancy BMI. They showed low circulating Arginine levels which seem related to poor pregnancy outcome [79].

Finally, in ovine, swine and equines, L-Arg supplementation also improved the reproductive performances becoming one among the interventions able to increase animal production.

Among the studies included, in this review none reported serious adverse reactions to L-Arg supplementation thus confirming a previously reported safety profile in pregnancy [72]. Severe adverse events were reported only in a population of patients with a recent coronary heart disease over a long-term treatment (6 months) at high dose (9 g/day) [74]. Moreover, in a controlled study, L-Arg has been found safe in subjects ingesting 15–30 g/day for 90 days, with no impact on the intake of energy, protein, carbohydrates, vitamins, or minerals. However, it is worth mentioning that NO donor supplementation in pregnancy is still debated, as not all NO donors are considered safe in pregnancy. Sildenafil, for example, when administered for severe early-onset fetal growth retardation, not only did not reduce the risk of perinatal mortality or severe neonatal morbidity, but actually increased the risk of neonatal pulmonary hypertension [75].

Arginine is a non-essential amino acid whose intake from the diet (meats, dairy products, nuts, …) has been estimated to be >4 g/day in western countries [76] while it seems much less available in people living in low resource settings [77]. For a lot of micronutrients, such as iron, iodine, calcium, Vitamin D, and so on, pregnancy represents a status of relative deficiency [78]. Thus, although we lack standard of Arg intake in pregnancy, it seems not unlikely that during gestation women require more intake due to both major needs (fetal growth) and to cover changes in eating behavior (i.e. less intake of meat).

Furthermore, L-Arg administered intravenously was associated with important fetal and maternal vascular effects [18, 32]. However, the effects were not long-lasting, and the clinical feasibility was poor allowing oral Arginine be preferred in clinical trials.

However, the evidence highlighted in this systematic review indicate that L-Arg displays biological activities supporting its potential as a "therapeutic agent." Moreover, neither human, nor animal ingestion of L-Arg have been associated to side effects and/or adverse reactions, at the given doses.

The "novelty" of this systematic review is that it examined not only the vascular but also the metabolic effect of arginine, including both animal and human studies. In particular, the L-NAME model was evaluated to target the well-consolidated, NO-mediated L-Arg action. The hyperinsulinemia animal model, on the other hand, allows for the first time to transfer the possible metabolic effects to pregnancy, which have not yet been well studied, contrary to non-pregnant conditions where various evidence of the metabolic impact of arginine is already available both in experimental [80, 81] and human studies [81–83].

Nitric oxide (NO) is a key regulator of both maternal and fetal homeostasis during pregnancy nevertheless

strategies involving supplementation with NO precursors, NO donors, natural derivatives or pharmacological modulators of the NO system need to be more evaluated and randomized trials are yet warranted. This review suggests that the supplementation of a certain kind of L-Arg (i.e. in intravenous form or in oral vial as salt free form at a dose of 3 g/day) may not simply be used as a replacement for a transitory deficiency. Instead, through its cardiovascular and metabolic effects, L-Arg could be candidate as an intervention beneficial to maternal and fetal outcomes, at least in moderate clinical disorders.

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