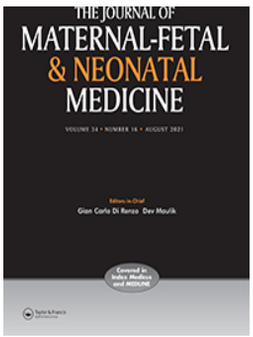

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ORIGINAL ARTICLE

Conservative management of early-onset severe preeclampsia: comparison between randomized and observational studies a systematic review

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ABSTRACT

Objective: To compare maternal and perinatal outcomes between randomized trials and observational studies in which conservative management was performed for more than 48 h in patients with early-onset severe preeclampsia.

Methodology: We searched PubMed, LILACS, Cochrane and Google Scholar. The studies were divided in two groups: randomized and observational studies, from 1990 to 2018 that included patients with severe preeclampsia before 34 weeks of gestation with pregnancy prolongation ≥48 h but that did not include fetal growth restriction or HELLP syndrome at the beginning. The main variables recorded were maternal and perinatal complications.

Main Results: Forty-four studies met the inclusion criteria, and 5 of these were randomized. The average pregnancy prolongation was 9 days, with no difference between groups. Maternal complications were significantly more common in observational studies, RR = 0.71, 95% CI (0.54–0.93), $p = .009$. Perinatal complications were also significantly more common in observational studies (RR = 0.89, 95% CI (0.80–0.98), $p = .01$) at the expense of stillbirth and neonatal deaths. The percentages of cesarean sections were significantly higher in randomized studies, RR = 1.54, 95% CI (1.46–1.64). There were 2 maternal deaths, both in observational studies.

Conclusion: Observational studies in which conservative management of early-onset preeclampsia is performed and do not include patients with fetal growth restriction or patients with HELLP syndrome and where at least 2 days of pregnancy prolongation is achieved are associated with significantly more maternal and perinatal complications.

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Randomized controlled trial; observational trial; conservative management; severe preeclampsia; early-onset severe preeclampsia; HELLP syndrome; stillbirth

Introduction

Preeclampsia is a condition that only occurs during pregnancy; it is characterized by hypertension occurring for the first time accompanied by proteinuria after 20 weeks of pregnancy and is estimated to affect between 2 and 5% of pregnant women [1]. Preeclampsia can be subdivided into early-onset preeclampsia (birth <34 weeks of gestation) and late-onset preeclampsia (birth ≥34 weeks of gestation) [1]. Recently, in a study with more than half a million pregnant women during a period of 10 years in Norway [2], it was found that the incidence of early-onset preeclampsia is one in every 200 pregnant women (0.5%), representing 13% of all preeclampsia cases. However, the percentage of early-onset severe preeclampsia is unknown.

The treatment or cure for preeclampsia is termination of pregnancy [3], particularly if the patient meets the criteria for severe preeclampsia [4]. If a pregnant woman has early-onset severe preeclampsia, management becomes a dilemma for the clinician because of the possibility of maternal complications such as placental abruption, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, disseminated intravascular coagulation, eclampsia, renal failure, hepatic hematoma/rupture, pulmonary edema and maternal death [5] and fetal or neonatal complications such as growth restriction, respiratory distress syndrome, intraventricular hemorrhage, neurological damage, and intrauterine and neonatal death [6] with or without the termination of pregnancy. Three decades ago, the first randomized study was published suggesting a neonatal benefit without harming the mother when

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conservatively managing patients with severe preeclampsia before 34 weeks of gestation [7]. However, a similar study [8] with more patients was recently published and showed no perinatal benefits with conservative management compared with aggressive management; on the contrary, conservative management was associated with increased fetal growth restriction and increased placental abruption [8].

The most recent Cochrane systematic review [6] on the management of early-onset severe preeclampsia concludes that with the few existing randomized studies, expectant management is associated with a decrease in neonatal morbidity. We do not know if observational studies lead to the same results.

The objective of this historical review is to compare maternal and perinatal outcomes between randomized controlled trials (RCTs) and observational studies where conservative management was performed for more than 48 h in patients with early-onset severe preeclampsia ($\leq$ 34 weeks) without growth restriction and without HELLP syndrome and compare results.

Materials and methods

This research is a systematic review with the following inclusion criteria: all RCTs and observational studies or case series from 1990 to 2018 that included patients with severe preeclampsia at 34 or fewer weeks of gestation where pregnancy was prolonged by 48 or more hours, in which patients with fetal growth restriction or HELLP syndrome were not included at the beginning of the study. If fetal growth was used to definition of severe preeclampsia the study was excluded.

We searched the online databases PubMed, LILACS, Cochrane and Google Scholar for studies that included the established inclusion criteria. We used the following search strategy (in all fields): ("gestational hypertensive disorder" OR "pregnancy-induced hypertension" OR ("pre-eclampsia" or "preeclampsia") OR "hypertension" AND "pregnancy" AND "early intervention," "early birth," "interventionist," "conservative," "active management," "conservative management," "expectant management," "aggressive management," "conservative treatment") with the search limits "human." In addition, references from, review articles, and clinical guidelines were reviewed looking for possible studies. Complete studies published in English, Portuguese and Spanish were reviewed, in addition to the English abstract of studies published in other languages, which were translated into English if included in the review.

Main results: Each study selected after meeting the inclusion criteria had the following information added to a database: type of study (randomized or observational), year of publication, country where it was performed, whether the country was industrialized, total patients, gestational age, duration of pregnancy prolongation, most frequently reported maternal complications (placental abruption, HELLP syndrome, renal failure, intravascular coagulation, acute pulmonary edema, eclampsia, maternal death), most frequently reported perinatal complications (fetal growth restriction, intrauterine death), perinatal death (intrauterine death plus neonatal death), intraventricular hemorrhage, respiratory distress syndrome, whether the cause for the interruption was maternal or fetal, and how the pregnancy was terminated. Of the RCTs, only the group that received expectant management was analyzed. Some women and some neonates had more than one complication, and the total number of complications was recorded.

We report in accordance with the PRISMA-IPD statement.

Statistical analysis: The statistical analysis was performed using EPI Info version 7 (Centers for Disease Control and Prevention, Atlanta, GA). For each variable, the results of all studies were compared between RCTs and observational studies. In addition, the pregnancy outcomes were compared from 28 to 34 weeks, and results were compared between countries according to per capita income. For the analyses, Fisher's exact test or the chi-squared test was used as appropriate, and the risk ratio (RR) was calculated with the 95% confidence interval (CI). p values less than .05 were considered significant.

Results

For the 29-year period from 1990 through 2018, 44 studies met the inclusion criteria, of which 5 were RCTs [7–11] (Figure 1 and Table 1). Of the 5 RCTs, 2 were conducted in countries with a high per capita income, and of the 39 observational studies [5,12–49], 21 were in countries with a medium or low per capita income. The countries with the highest per capita income and more publications were the USA, Japan and the Netherlands, and those with a low and medium per capita income and more publications were South Africa, India, and Mexico. The study with the most patients (340) was performed in South Africa [16], and that with the fewest patients (10) was conducted in Thailand [33]. The total number of patients for RCTs and observational studies was 243 and 2740,

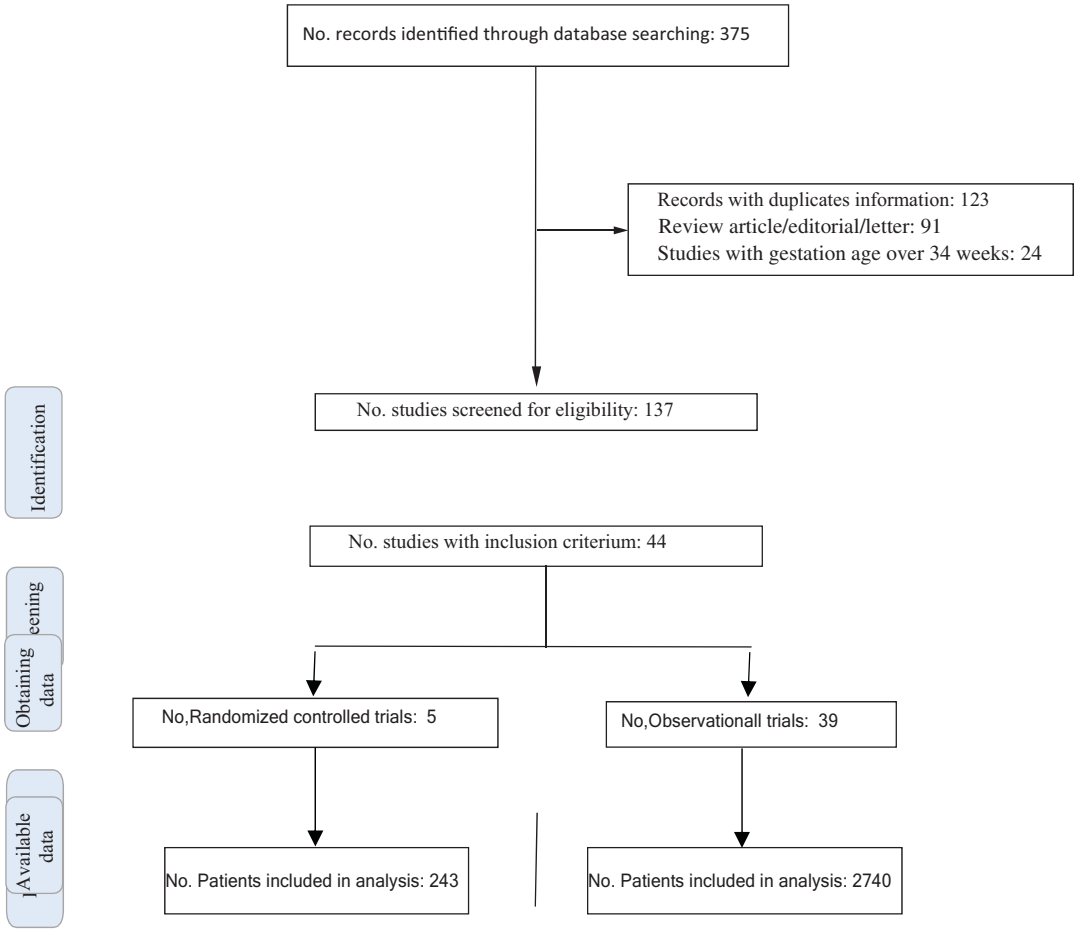

Figure 1. Flow diagram–summary of evidence search and analysis.

respectively (Table 2). The average duration of pregnancy prolongation was 9 days and was very similar between randomized trials and observational studies.

Maternal complications were significantly more common in observational studies, RR = 0.71, 95% CI (0.54–0.93), $p = .009$; severe complications were predominant, such as renal failure, pulmonary edema and eclampsia (Table 3). This difference is maintained when we analyze studies conducted in high per capita income countries, but it is not observed if we only analyze studies conducted in medium and low per capita income countries. Furthermore, no significant differences were observed with maternal complications when comparing RCTs with observational studies that only included patients between 28 and 34 weeks of gestation (Table 4).

Perinatal complications were also significantly more common in observational studies (RR = 0.89, 95% CI (0.80–0.98), $p = .01$), at the expense of fetal deaths (intrauterine) and postnatal deaths (Table 2). When we analyzed intrauterine deaths and perinatal deaths (intrauterine plus postnatal) between both types of studies for gestational ages from 28 to 34 weeks, in countries with high per capita income and in countries with medium and low per capita income, there were significantly more deaths in observational studies (Table 4).

The percentages of cesarean sections were significantly higher in RCTs, RR = 1.54, 95% CI (1.46–1.64). This difference was always maintained in favor of RCTs if we only analyzed studies that investigated gestational ages between 28 and 34 weeks, if we only analyzed studies from high per capita income countries or if we only analyzed studies from low- and middle-income countries.

In the RCTs, the main cause of pregnancy interruption was maternal in 59.2% of cases. In observational studies, the main cause of pregnancy interruption was also maternal but only in 27% of cases, $p = .0001$.

In this review, there were 2 maternal deaths, both in observational studies of nonindustrialized countries.

Discussion

This historical review of RCTs and observational studies with conservative management of early-onset

Table 1. Studies included in the review.

Study	Design	Country	Sample size (conservative management)
Odendaal 1990 [7]	RCT	South Africa	18
Sibai 1994 [9]	RCT	USA	49
Mesbah 2003 [10]	RCT	Egypt	15
Vigil-De Gracia [8]	RCT	Latin America	131
Duvekot [11]	RCT	Netherlands	30
Sibai 1990 [12]	Observational	USA	69
Moodley 1993 [13]	Observational	South Africa	50
Olah 1993 [14]	Observational	UK	28
Chammas 2000 [15]	Observational	USA	33
Hall 2000 [16]	Observational	South Africa	340
Romero 2000 [17]	Observational	Mexico	34
Murphy 2000 [18]	Observational	UK	71
Blackwell 2002 [19]	Observational	USA	63
Kobayashi 2003 [20]	Observational	Japan	29
Vigil-De Gracia 2003 [21]	Observational	Panama	129
Haddad 2004 [22]	Observational	France	239
Oettle 2005 [23]	Observational	South Africa	121
Shear 2005 [24]	Observational	Canada	59
Budden 2006 [25]	Observational	New Zeland	31
Hall 2006 [26]	Observational	South Africa	82
Gaugler-Senden 2006 [27]	Observational	Netherlands	16
Porras-Poma 2006 [28]	Observational	Peru	79
Ganzevoort 2007 [29]	Observational	Netherlands	80
Sezik 2007 [30]	Observational	Turkey	55
Bombrys 2008 [31]	Observational	USA	46
Sarsam 2008 [32]	Observational	Iraq	35
Jantasing 2008 [33]	Observational	Thailand	10
Bombrys 2009 [34]	Observational	USA	66
Abdel-Hady 2010 [35]	Observational	Egypt	211
Mogollon-Saker 2011 [36]	Observational	Colombia	24
Belghiti 2011 [37]	Observational	France	51
Kumar 2011 [38]	Observational	India	45
Swamy 2012 [39]	Observational	India	94
Astudillo 2013 [40]	Observational	Spain	33
Castellon-Pasos 2013 [41]	Observational	Mexico	27
Chen 2015 [42]	Observational	China	79
Suzuki 2014 [43]	Observational	Japan	30
Ertekin 2015 [44]	Observational	Turkey	33
Rendon-Becerra 2016 [45]	Observational	Colombia	31
Emawati 2016 [46]	Observational	Indonesia	44
Ueda 2016 [47]	Observational	Japan	41
McKinney 2016 [5]	Observational	USA	116
Deepak 2017 [48]	Observational	India	76
Vazquez-Rodríguez 2018 [49]	Observational	Mexico	40

Table 2. General information of randomized controlled trials and observational studies with conservative management of early-onset severe preeclampsia.

VARIABLE	RCT	OS	TOTAL
Number of studies *n*	5	39	44
Total number of patients *n*	243	2740	2983
Pregnancy prolongation, days (range)	8.8 (3.0–15.4)	9.5(2.3–32.7)	9.2(2.3–32.7)
Industrialized country *n*	2	18	20
Nonindustrialized country *n*	3	21	24
Years 1990–1999 *n*	2	3	5
Years 2000–2009 *n*	1	20	21
Years 2010–2018 *n*	2	16	18

RCT: Randomized controlled trial; OS: Observational study.

severe preeclampsia shows that maternal and perinatal complications are statistically more common in nonrandomized studies. Perinatal mortality and, especially, intrauterine (fetal) mortality are more common in observational studies, regardless of level of development of the country where the study was conducted. The frequency of cesarean sections in RCTs was 90%, approximately 30% higher than that in observational studies.

The best clinical practice is based on the results obtained from RCTs. The first RCT [7] on the conservative management of early-onset severe preeclampsia was published in December 1990, and the second was published in 1994 [9]. These 2 studies led to the

Table 3. Main maternal and perinatal outcomes of randomized controlled trials and observational studies with conservative management of early-onset severe preeclampsia.

VARIABLE	RCT (243)	OS (2740)	RR 95% CI	*p*
Maternal complications *n*(%)	47(19.3)	741(27.0)	0.71(0.54–0.93)	.009
Placental abruption *n*(%)	17(7.0)	211(7.7)	0.90(0.60–1.50)	.69
HELLP syndrome *n*(%)	22(9.0)	326(11.9)	0.76(0.50–1.15)	.18
Acute pulmonary edema *n*(%)	3(1.2)	65(2.3)	0.52(0.16–1.64)	.25
Renal failure *n*(%)	4(1.6)	110(4.0)	0.41(0.15–0.99)	.02
Eclampsia *n*(%)	1(0.4)	27(1.0)	0.42(0.05–3.06)	.37
Maternal death *n*	0	2	–	.67
Perinatal complication *n*(%)	150(61.7)	1900(69.3)	0.89(0.80–0.98)	.01
Respiratory distress syndrome *n*(%)	73(30.0)	426(15.5)	1.93(1.56–2.38)	.0001
Intraventricular hemorrhage *n*(%)	2(0.8)	63(2.2)	0.36(0.04–1.34)	.16
Restriction of fetal growth *n*(%)	54(22.2)	572(20.9)	1.06(0.83–1.36)	.62
Intrauterine death *n*(%)	2(0.8)	309(11.2)	0.07(0.01–0.29)	.0001
Perinatal mortality *n*(%)	19(7.8)	530(19.3)	0.40(0.26–0.62)	.0001
Cesarean sections *n*(%)	211(87.0)	1537(56.0)	1.54(1.46–1.64)	.0001

RCT: Randomized controlled trial; OS: Observational study.

Table 4. Maternal and perinatal outcomes of randomized controlled trials and observational studies with conservative management of early-onset severe preeclampsia.

VARIABLE	RCT	OS	RR 95% CI	*p*
Gestational age 28–34 weeks *n*	243	639	–	–
Total number of studies analyzed *n*	5	8	–	–
Total maternal complication *n*(%)	47(19.3)	120(18.8)	1.02(0.76–1.39)	.84
Total perinatal complication *n*(%)	150(61.7)	440(69.0)	0.89(0.80–1.0)	.04
Intrauterine death *n*(%)	2(0.8)	49(7.7)	0.10(0.02–0.43)	.0001
Perinatal mortality *n*(%)	19(7.8)	99(15.4)	0.50(0.31–0.80)	.002
Cesarean section *n*(%)	211(87.0)	351(55.0)	1.58(1.45–1.72)	.0001
Industrialized countries $\leq$ 34 weeks	*n* = 79	*n* = 1101	–	–
Total number of studies analyzed *n*	2	18	–	–
Total maternal complication *n*(%)	6(7.6)	356(32.3)	0.23(0.10–0.50)	.0001
Total perinatal complication *n*(%)	28(35.4)	775(70.3)	0.50(0.37–0.68)	.0001
Intrauterine death *n*(%)	0	102(9.2)	Lack	.001
Perinatal death *n*(%)	1(1.2)	179(16.2)	0.07(0.01–0.54)	.0003
Cesarean *n*(%)	63(79.7)	715(64.9)	1.22(1.08–1.38)	.007
Nonindustrialized countries $\leq$ 34 weeks	*n* = 164	*n* = 1639	–	–
Total number of studies analyzed *n*	3	21	–	–
Total maternal complication *n*(%)	40(24.3)	393(24.0)	1.01(0.77–1.34)	.90
Total perinatal complication *n*(%)	120(73.1)	816(49.8)	1.45(1.32–1.63)	.0001
Intrauterine death *n*(%)	2(1.2)	207(12.6)	0.10(0.02–0.38)	.0001
Perinatal death *n*(%)	18(11.0)	352(21.4)	0.51(0.32–0.80)	.001
Cesarean *n*(%)	148(90.2)	819(50.0)	1.80(1.68–1.93)	.0001

RCT: Randomized controlled trial; OS: Observational study. Subanalysis at only 28–34 weeks and subanalysis of the entire population between countries according to per capita income.

conservative management of early-onset severe preeclampsia in clinical practice, which was confirmed through the publication of 30 observational studies [12–41] until the end of 2013, when the RCT [8] with the largest number of patients was published. The results of that RCT were not encouraging for the conservative management of early-onset severe preeclampsia.

To our knowledge and certainly of any clinician in the world, the results of observational studies (cohorts, historical cohorts, case-controls, case series) should find similar results than do RCTs. There are great differences when comparing observational studies with RCTs, but if only are results that are easy to measure, are universally defined in the exact same way and are reported in all randomized and observational studies are analyze, we can achieve relevant clinical conclusions. However, the observational studies analyzed in this review show great heterogeneity and therefore the results should be interpreted with great caution.

The sum of maternal complications in RCTs are not different when comparing conservative versus aggressive management [6]; however, maternal complications are much more common in observational studies; therefore, they equate to higher percentages, with significant differences, than those in RCTs with groups undergoing expectant or aggressive management. This difference, of more maternal complications in observational studies, is up to 4 times higher in studies from high-income countries. Our review found 2 maternal deaths, both in observational studies, and we consider this finding to be unacceptable and unjustifiable.

Interestingly, the percentages of cesarean sections are very high, with a significant difference favoring RCTs [7–11]. Possibly due to the nature of these

studies, there is a much more aggressive behavior at the time of pregnancy termination; it is likely that this aggressive behavior and strict surveillance explains the few fetal and neonatal deaths between the expectant and interventionist groups in RCTs [7–11] and probably also explains the existence of fewer maternal complications in RCTs than in observational studies, and it is possible a Hawthorne effect.

One of the most important variables to report in studies with conservative management of severe preeclampsia far from term is perinatal mortality (stillbirth and neonatal death). Our analysis allows us to conclude that 2.4 times more fetuses and neonates die in observational studies than in randomized studies, regardless of gestational age and level of development of the country where the study was conducted. Recently, in Norway [2], a study reported a relative risk of fetal death by preeclampsia ranging from 11.6 at 26 weeks to 1.1 at 34 weeks for every 1000 women, with a risk of fetal death of approximately 3.0 for every 1000 women with preeclampsia at $\leq$ 34 weeks of gestation. Our review finds that the risks of fetal death in RCTs and observational studies is 8.2 for every 1000 women and 113 for every 1000 women, respectively.

However, our study did not stratify by gestational age and, as is obvious, there are enormous differences in the two types of studies.

Unfortunately, the majority of observational studies [12,13,15–32,39,46–48] suggest conservative management of early-onset preeclampsia; others question that option [14,38,43–45,49], particularly after the MEXPRE Latin study [8].

The practice of medicine today depends largely on the results of studies with better evidence; the expectant management of early-onset severe preeclampsia has been based on low or very low evidence [3,6]. Interestingly, for each randomized study, there are approximately 8 observational studies, and the vast majority of these studies suggest expectant management. This means that it is possible that the majority of hospitals around the world, based on the few randomized studies and on many observational studies, perform expectant management as routine management protocols. Unfortunately, this review demonstrates that the maternal and perinatal outcomes of observational studies are worse than those of randomized studies.

A strength of this review is the number of studies (44) and patients analyzed (2983), representing 3 decades of research and reports from different countries around the world. Another strength is that the findings with differences show high statistical value and are maintained despite different gestational age groups or levels of country development. Yet another strength is the comparison of strict follow-up studies (RCTs) with studies reporting daily life or actual practice observational studies.

The limitations of this research include the nature of the review because results from randomized studies are compared with those from observational studies, which is questionable. Another limitation is the possibility that some studies were not found by the search engines used. The span of the study (29 years) may introduce biases, not only in the definition of severe preeclampsia used, but also in the improvements in neonatal care.

In summary, observational studies in which conservative management of early-onset preeclampsia is performed and do not include patients with fetal growth restriction nor patients with HELLP syndrome and in which pregnancy is prolonged for at least 2 days are associated with a significantly greater number of maternal complications and perinatal deaths (fetal and neonatal). The results of this study should be interpreted with great caution since there are great differences in the methodologies of observational and randomized studies. Large and very rigorous randomized studies are necessary to define the best management of patients with severe pre-eclampsia far from the term.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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