Systematic review of black cohosh (*cimicifuga racemosa*) for management of polycystic ovary syndrome-related infertility

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Introduction

- Polycystic ovary syndrome (PCOS) affects as many as 5 million women of reproductive age in the United States.[1]
- The diagnosis of PCOS is defined by the Rotterdam criteria as meeting two of the following[2-3]:
  - Oligo and/or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries
- Current guidelines recommend letrozole as the first-line pharmacologic treatment for PCOS-related anovulatory infertility.[4-5] Clomiphene citrate (CC) may alternatively be used.
- Adverse effects of these agents may include multiple births, hot flashes, headache, dizziness, upset stomach, and ovarian hyperstimulation syndrome (OHSS).[6-7]
- Black cohosh (BC) (*cimicifuga racemosa)* is a natural phytoestrogen product studied as an adjunct or alternative to CC for PCOS-related infertility through potential regulation of the luteinizing hormone to follicle-stimulating hormone (LH/FSH) ratio and subsequent ovulation induction.[8]
- Adverse effects of black cohosh include stomach upset, cramps, headache, rash, weight gain[8]; and potentially hepatotoxicity and liver transplant.[9]

Objective

- Assess the efficacy and safety of black cohosh for ovulation induction to improve pregnancy rates in women with PCOS-related infertility.

Methods

Table 1 – Search Terms

PCOS	PCOS OR polycystic ovarian syndrome OR polycystic ovary syndrome OR sclerocystic ovarian degeneration OR sclerocystic ovaries OR sclerocystic ovary OR sclerocystic ovary syndrome OR stein leventhal syndrome OR stein-leventhal syndrome
Black Cohosh	Black cohosh OR Actaea racemosa OR Cimicifuga racemosa OR Actaea macrotys OR Actee a Grappes OR Actee a Grappes Noires OR Actee Noire OR Aristolochiaceae Noire OR Baie dactee OR Baneberry OR Black Aristolochiaceae OR Black Snakeroot OR Bugbane OR Bugwort OR Cimicaire a grappes OR Cimicifuga OR Cimicifuge OR Cohosh Negro OR Cohosh Noir OR Cytise OR Herbe aux Punaises OR Macrotys OR Racine de Serpent OR Racine de Squaw OR Racine Noire de Serpents OR Rattle Root OR Rattle Top OR Rattlesnake Root OR Rattleweed OR Rhizoma Cimicifugae OR Sheng Ma OR Snakeroot OR Squaw Root

Methods

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used to develop and report study methods.[10]
- A search of Medline, Embase, International Pharmaceutical Abstracts, Cumulative Index of Nursing and Allied Health Literature, and ScienceDirect spanning origin to May 28, 2020, sought records relevant to this review.
- Inclusion criteria for the database searches consisted of reported efficacy and/or safety data on black cohosh; conducted in women with PCOS and infertility; full text available in English; and, identified as published primary literature.
- Exclusion criteria for the database searches consisted of abstract-only publications.
- Manual bibliographic review was performed for the two relevant studies.[11-12]
- Additional searches were conducted for National Clinical Trials (NCT) database and the International Clinical Trials Registry Platform (ICTPR) to identify randomized controlled trials (RCTs) meeting the inclusion criteria using the search term, "PCOS".[13-14]
- Identified literatures were assessed for risk-of-bias via the Cochrane Risk of Bias of Randomized Studies of Interventions Assessment Tool (RoB2) for RCTs.[15]

Results

Table 2 – Participant Demographics[11-12]

	Kamel 2013		Shahin et al. 2014	
	CC	BC	CC	BC+CC
Age (years)	24 ± 2.66	23 ± 2.3	28.7 ± 2.8	27.6 ± 2.9
Body Mass Index (kg/m^2)	25 ± 2.33	26 ± 1.7	26 ± 1.8	27 ± 2.2
Primary Infertility	39 (52%)	36 (48%)	86/98 (87.8%)	80/96 (83.3%)
Secondary Infertility	11 (44%)	14 (56%)	12/98 (12.2%)	16/96 (14.6%)

- 182 records resulted from the five databases and 158 records were manually screened after deduplication. A total of two studies have met the eligibility criteria and have reported efficacy and safety outcomes.[11-12]
- No additional studies were identified from the bibliographic review.
- 1321 records were found from the 18 clinical trial registries and 3 studies were identified for inclusion.[16-18] However, one has a completion status without publications, another has an unknown recruitment status, while the other is in active recruitment. Thus, none of which have available publications.

Results

Table 3 – Interventions[11-12,16-18]

	Black cohosh group	Comparator group(s)
Kamel	*Cimicifuga racemosa* (Klimadynon®) 20 mg PO BID on cycle day 2 for 10 days. Repeat for three successive cycles.	CC 50 mg PO BID for 5 days starting on cycle day 2. Repeat for three successive cycles.
Shahin et al.	CC 150 mg/day PO on cycle days 3-7 plus *cimicifuga racemosa* (Klimadynon®) 120 mg/day PO on cycle day 1 through day of pregnancy test or menstruation.	CC 150 mg/day PO on cycle days 3-7.
Maged	*Cimicifuga racemosa* (Klimadynon®) 20 mg on cycle days 1-12 plus CC 50 mg PO q8h on cycle day 3 for 5 days.	CC group: CC 50 mg PO q8h on cycle day 3 for 5 days. EV+CC group: estradiol valerate (EV) 2 mg on cycle days 7-11 plus CC 50 mg PO q8h on cycle day 3 for 5 days.
Hashish	*Cimicifuga racemosa* (Klimadynon®) 120 mg/day (2 tablets TID) on cycle days 1-12 plus CC 100 mg/day PO on cycle day 5 for 5 days.	IM + CC group: isosorbide mononitrate (IM) 20 mg tablet applied vaginally on cycle days 1-12 plus CC 100 mg/day PO. NAC + CC group: N-Acetyl cysteine 1200 mg/day PO (two 200 mg sachets TID) on cycle days 1-12 of plus CC 100 mg/day PO.
Elkateeb	*Cimicifuga racemosa* (Klimadynon®) 20 mg PO BID on cycle day 7 plus CC 50 mg PO BID until the time of hCG injection.	CC 50 mg PO BID for 5 days.

Table 4 – Efficacy and Safety Outcomes[11-12]

	Kamel 2013 (After cycle 1, cycle 2, cycle 3)		Shahin et al. 2014	
	CC	BC	CC	BC+CC
FSH/LH Ratio	1.7 ± 0.73, 1.3 ± 0.55, 0.805 ± 0.82	1.03 ± 0.98, 1.05 ± 0.34, 0.582 ± 0.21	NR	NR
Endometrial Thickness (mm)	6.89, 6.34, 7.32	8.34, 9.67, 9.11	8.5 ± 1.9	12.5 ± 1.9
Pregnancy†	1, 2, 1	2, 3, 2	38/192 (19.8%)	78/204 (38.2%)
OHSS	0, 1, 1	1, 0, 0	NR	NR
Miscarriage†	NR	NR	5/192 (2.6%)	6/204 (2.9%)
Abortion	0	1	NR	NR
Multiple births†	2	1	2 (1.0%)	3 (1.3%)

*NR = Not recorded
† = measured per cycle in Shahin et al. 2014[12]

Results

Table 5 – Risk of Bias (ROB) Assessment[11-12]

	Kamel	Shahin et al.
Randomization process	High risk	High risk
Deviations from intended interventions	Low risk	Low risk
Missing outcome data	Low risk	Low risk
Measurement of the outcome	Low risk	Low risk
Selection of the reported result	Low risk	Low risk
Overall bias	High risk	High risk

Kamel Limitations: power; treatment regimen; eligibility criteria; blinding; author's conclusions

Shahin et al. Limitations: blinding

Conclusion

- There is no high-quality evidence to support the effectiveness of black cohosh in improving pregnancy rates in women with PCOS-related infertility.
- There is limited data demonstrating the safety of use of black cohosh in this population. It appears to be safe in the studies[11-12], however, further investigations into the safety data, including the hepatic effects are needed.
- Surrogate markers such as normalization of LH/FSH ratio and increase in endometrial thickness may not necessarily translate into a successful pregnancy. Efficacy outcomes such as pregnancy rates and live birth rates may be more relevant.
- The three studies from the clinical trial registries have not been published and may not contribute much literature to future decision making.[16-18]
- Future research directions may include evaluating the effect of black cohosh as an adjunct therapy with letrozole or alternative to letrozole in this patient population.
- It may be important for future studies to justify dosing selection and investigate the possible drug interaction between letrozole or clomiphene citrate and black cohosh that may warrant dose adjustments.

Disclosures

Authors of this presentation have the following to disclose concerning the possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Chi Wai Fan, Nicole E. Cieri-Hutcherson, Timothy C. Hutcherson: Nothing to disclose

Selected References

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