Appendix 1. Search Terms by Sets of Concepts

Set #	Concept	PubMed Search Statements
1	Contraception	Contracept*[All fields]
2	Injectable contraceptive method	Injectable*[All fields] OR Injection*[All fields] OR “Depo Provera”[All fields] OR “Depo-Provera”[All fields] OR “Depo Ralovera”[All fields] OR Megestron[All fields] OR Petogen[All fields] OR “medroxyprogesterone acetate”[MeSH] OR “medroxyprogesterone acetate”[All fields] OR “Depomedroxyprogesterone acetate”[All fields] OR “depot medroxyprogesterone acetate”[All fields] OR DMPA[All fields]
3	Side effects (beneficial or harmful) listed in WHO Handbook for at least one contraceptive method, some common health risks from the WHO Handbook, side effects included in the FDA birth control chart, as well as other common health-related concerns women have	Menstruation[MeSH] OR Menstruation[All fields] OR “Menstrual bleeding”[All fields] OR “Menstrual spotting”[All fields] OR “Menstrual cramps”[All fields] OR Amenorrhea[MeSH] OR Amenorrhea[All fields] OR Oligomenorrhea[MeSH] OR Oligomenorrhea[All fields] OR Metrorrhagia[MeSH] OR Metrorrhagia[All fields] OR Menorrhagia[MeSH] OR Menorrhagia[All fields] OR Dysmenorrhea[MeSH] OR Dysmenorrhea[All fields] OR “Ovulation pain”[All fields] OR Mittelschmerz[All fields] OR “Heavy menstrual bleeding”[All fields] OR “Abdominal bloating”[All fields] OR “Abdominal discomfort”[All fields] OR “Abdominal pain”[MeSH] OR “Abdominal pain”[All fields] OR Headaches[MeSH] OR Headaches[All fields] OR Dizziness[MeSH] OR Dizziness[All fields] OR Nausea[MeSH] OR Nausea[All fields] OR Vomiting[MeSH] OR Vomiting[All fields] OR Fatigue[MeSH] OR Fatigue[All fields] OR “Influenza, Human”[MeSH] OR Influenza[All fields] OR “Upper respiratory infection”[All fields] OR “Acne Vulgaris”[MeSH] OR “Acne Vulgaris”[All fields] OR “Body weight”[MeSH] OR “Body weight”[All fields] OR “Body weight changes”[MeSH] OR “Body weight changes”[All fields] OR “Breast tenderness”[All fields] OR “Breast pain”[All fields] OR “Hair loss”[All fields] OR Alopecia[MeSH] OR Alopecia[All fields] OR “Skin irritation”[All fields] OR Rash[All fields] OR

Dianat S, Fox E, Ahrens KA, Upadhhyay UD, Zlidar VM, Gallo MF, et al. Side effects and health benefits of depot medroxyprogesterone acetate: a systematic review. Obstet Gynecol 2019; 133.
The authors provided this information as a supplement to their article.

Set #	Concept	PubMed Search Statements
		Vaginitis[MesH] OR Vaginitis[All fields] OR “Vaginal irritation”[All fields] OR “Vaginal discharge”[MeSH] OR “Vaginal discharge”[All fields] OR “Vaginal lesions”[All fields] OR “Vaginal dryness”[All fields] OR “Dyspareunia”[All fields] OR “Vaginosis, bacterial”[MesH] OR “Bacterial vaginosis”[All fields] OR Candidiasis[MeSH] OR Candidiasis[All fields] OR “Yeast infection”[All fields] OR “Urinary tract infections”[MeSH] OR “Urinary tract infections”[All fields] OR “Mood change”[All fields] OR “Mood disorder”[All fields] OR Depression[MeSH] OR Depression[All fields] OR “Anemia, Iron-deficiency”[MeSH] OR “Anemia, Iron-deficiency”[All fields] OR Anemia[MeSH] OR Anemia[All fields] OR “Sexual pleasure”[All fields] OR “Sex drive”[All fields] OR Libido[MeSH] OR Libido[All fields]
4	Health benefits include protection against certain diseases and conditions	Cancer[MeSH] OR Cancer[All fields] OR Neoplasms[MeSH] OR Neoplasms[All fields] OR “Ovarian cysts”[MeSH] OR “Ovarian cysts”[All fields] OR Infertility[MeSH] OR Infertility[All fields] OR “Premenstrual dysphoric disorder”[All fields] OR PMDD[All fields] OR Leiomyoma[MeSH] OR Leiomyoma[All fields] OR “Uterine fibroid”[All fields] OR “Endometrial hyperplasia”[All fields] OR “Pelvic inflammatory disease”[MeSH] OR “Pelvic inflammatory disease”[All fields] OR PID[All fields]
5	Combined set: side effects	(#1) AND (#2) AND (#3)*
6	Combined set: health benefits	(#1) AND (#2) AND (#4)*

Appendix 2. Criteria for inclusion and Exclusion of Studies

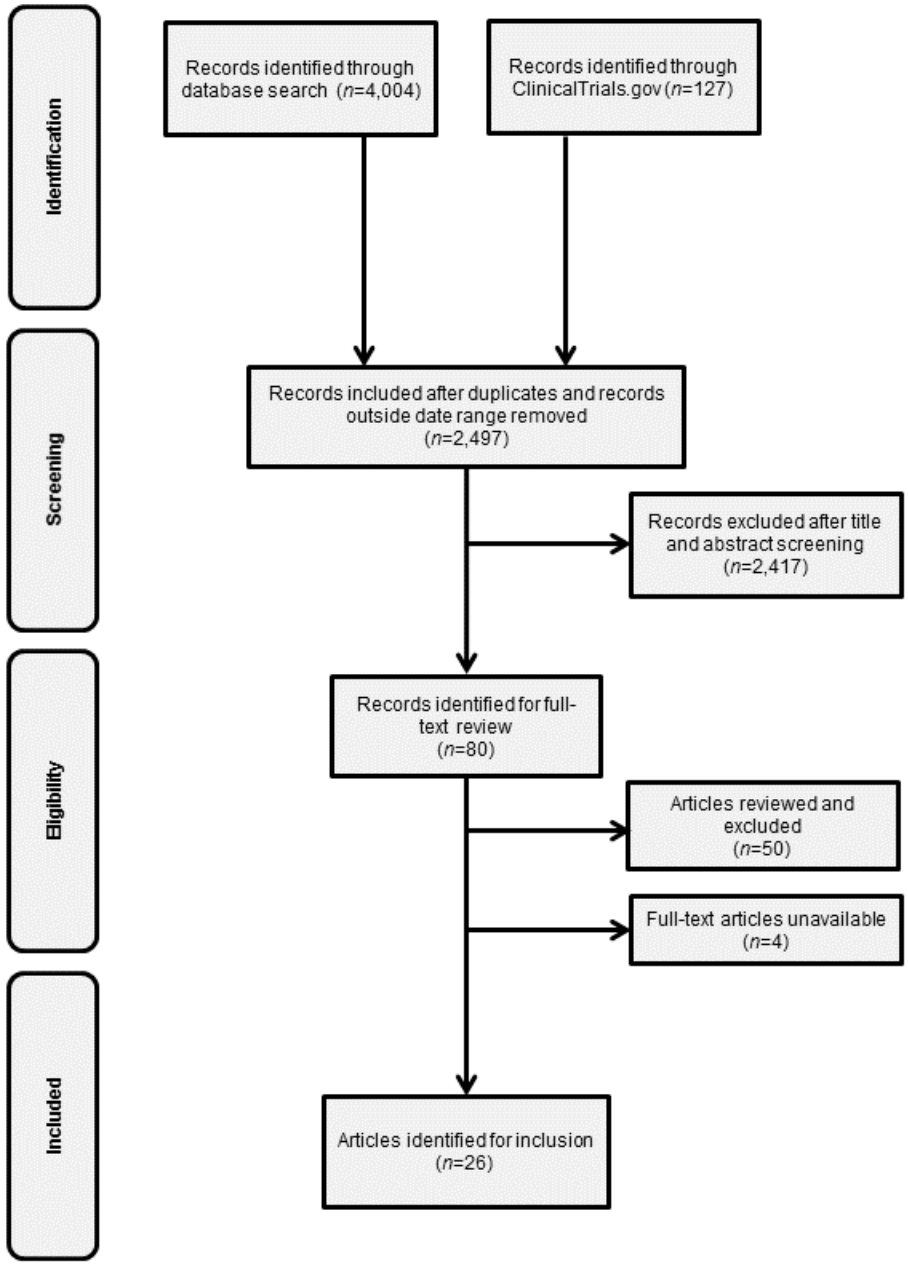
	KQ#	Inclusion Criteria	Exclusion Criteria
Populations	1 & 2	Non-breastfeeding, healthy women of reproductive age (13-49 years) at risk of unintended pregnancy.[1]	Other populations that fall outside of the target population
Interventions	1 & 2	Pre-determined regimen of injectable contraceptives, either self-administered or delivered by a provider, to assist clients in preventing unintended pregnancy	All other interventions that are not part of the targeted intervention being studied, including studies where injectable contraceptives are being used for purposes other than preventing unintended pregnancy
Comparators	1 & 2	A contemporaneous[2] non-hormonal or hormonal group assigned randomly, non-randomly, or based on observational data, to which the intervention group (injectable contraception use) is compared.	Studies with no comparison or control groups to which the targeted intervention can be compared for efficacy or effectiveness.
Outcomes	1	Side effects associated with injectable contraceptive use	Studies that do not estimate the association between injectable contraceptive use and relevant outcomes (i.e., studies regarding side effects not recognizable by patients or STD/HIV transmission)
	2	Health benefits associated with injectable contraceptive use	
Time Frames	1 & 2	Published between January 1, 1985 - November 30, 2016	Studies that fall outside of the predetermined date range
Settings	1 & 2	Clinical care or study settings (e.g., Federally Qualified Health Centers, public health clinics, school-based clinics, private doctor's offices, medical centers, University Centers etc.)	All other settings that fall outside of these settings
Study Design	1 & 2	Studies must have a two-group or multiple-group design with at least one group using injectable contraception and at least one eligible comparator; non-randomized controlled trial studies must also control for confounding in some way (covariate adjustment, restriction, stratification, re-weighting, etc.).	Studies that fall outside of the predetermined study design inclusion criteria (e.g., pre- and post-intervention studies with one group design, case series studies, comparison of study group with benchmark data)

[1] This criterion blends the following definitions: 1) Non-breastfeeding, healthy (average-risk) women of reproductive age using forms of contraception currently available in the US [from text], and 2) Healthy (low-risk) females aged 13-49 years at risk of unintended pregnancy. Post-partum women were excluded as a special population.

[2] Contemporaneous is defined here as a study cohort moving forward together in time; this is not a comparison of the same women pre- and post- contraceptive method use or a comparison group of women from another data source or time period. For rare outcomes, including some of the health risks and health benefits, a case control design can be considered a type of study nested within a cohort study and therefore included in the review.

Dianat S, Fox E, Ahrens KA, Upadhhyay UD, Zlidar VM, Gallo MF, et al. Side effects and health benefits of depot medroxyprogesterone acetate: a systematic review. Obstet Gynecol 2019; 133.
The authors provided this information as a supplement to their article.

Appendix 3. PRISMA flowchart of article identification, retrieval, review, and inclusion.



Appendix 4. Side Effects and Health Benefits Listed in the *WHO Family Planning Handbook*

Key Question 1 – Side Effects	Key Question 2 – Health Benefits
• Headaches • Dizziness • Fatigue • Nausea • Vomiting • Abdominal pain • Abdominal bloating and discomfort • Weight change • Weight gain • Mood changes • Acne (can improve or worsen) • Breast tenderness or pain • Reduced Libido • Skin irritation or rash at injection site • Flu symptoms or upper respiratory infection • Irritation, redness, or inflammation of the vagina (vaginitis) • Irritation in or around the vagina • White vaginal discharge • Vaginal lesions • No monthly bleeding (amenorrhea) • Lighter bleeding and fewer days of bleeding • Infrequent bleeding • Irregular bleeding • In breastfeeding women, longer delay in return of monthly bleeding after childbirth (lengthened postpartum amenorrhea) • Frequent bleeding • Prolonged bleeding • Prolonged and heavy monthly bleeding • More cramps and pain during monthly bleeding • Slight irregular bleeding for 1-2 days after taking ECPs • Monthly bleeding that starts earlier or later than expected • Blood pressure increase a few points (mm Hg) • Ovarian cysts • Loss of bone density (excluded because side effect not noticeable to patients) • Enlarged ovarian follicles	• Protection against iron-deficiency anemia • Protection against pelvic inflammatory disease (PID) • Protection against symptomatic pelvic inflammatory disease • Protection against recurring pelvic inflammatory disease and chronic pelvic pain • Reduces symptoms of endometriosis (pelvic pain, irregular bleeding) • Reduces ovulation pain • Protection against ovarian cysts • Protection against ovarian cancer • Reduces symptoms of polycystic ovarian syndrome (irregular bleeding, acne, excess hair on face or body) • Protection against cancer of the lining in the uterus (endometrial cancer) • Protection against cervical precancer and cancer • Protection against uterine fibroids • Protection against certain STIs (chlamydia, gonorrhea, pelvic inflammatory disease, trichomoniasis, HIV) • Protection against infertility caused by STIs • Reduces sickle cell crises among women with sickle cell anemia • Reduces menstrual cramps • Reduces menstrual bleeding problems • Reduces excess hair on face or body

Appendix 5. Side Effects and Health Benefits Examined by Study's Assessed Risk of Bias (26 Articles Reporting on 24 Studies and 61 Comparisons to DMPA)

Risk of bias	Number of comparisons to DMPA in total of 24 studies	Outcome of DMPA compared to comparison group	Increased weight or BMI	Increased body or central fat mass	Depressed or negative mood	Mood swings	Low libido or sexual interest	Cancer protection	Other
Moderate	19 comparisons in 11 studies	↑	Batista 2016* Clark 2005* Modesto 2014*†	Bonny 2009* Clark 2005*			Boozalis 2016*	Wilailak 2012 ‡	Ziaei 2004 (UTI)*
		↔	Dos Santos 2014* Dos Santos 2016*	Dos Santos 2014* Bonny 2009 §				Cuevas 1991 ‡	Bahamondes 1994 (all tubal infertility §, secondary tubal infertility*§) Dos Santos 2016 (binge eating disorder)*
		↓							Bahamondes 1994 (all tubal infertility)*
High	42 comparisons in 13 studies	↑	Bahamondes 2001* Berenson 2008*|| Berenson & Rahman 2009*§ Espey 2000 ‡ Nault 2013*|| Pantoja 2010* ¶	Berenson & Rahman 2009*§ Dal'Ava 2014*#	Civic 2000 ‡ Ott 2008 §		Berenson 2008* Schaffir 2010 §	Silpisornkosol 1991 ‡	Berenson 2008 (loss of energy, prolonged bleeding, spotting, amenorrhea)*
		↔	Dal'Ava 2014* Nault 2013 †|| Pantoja 2010* , ** Taneepanichskul 1998, 1999* Vickery 2013*††		Berenson 2008*	Brown 2008*§	Ott 2008 §		Berenson 2008 (acne, scalp hair loss, headache, hirsutism, dyspareunia, mastalgia)*
		↓				Berenson 2008*			Berenson 2008 (cramping, bloating)* Brown 2008 (well-being) *§

* compared to Cu-IUD or other mixed non-hormonal methods
† compared to progestin-only method
‡ compared to mixed non-DMPA methods
§ compared to combined hormonal contraceptive method(s)
|| perceived weight gain, which Nault (2013) found to have 75% sensitivity and 84% specificity for true weight gain
¶ normal- and overweight-BMI groups (counted as two comparison groups)
# DMPA users had greater increase in central fat but not in total body fat mass
** obese-BMI group

Appendix 6. Study Characteristics for References Reporting on Weight, Body Mass Index, or Body Composition

Author (Year)	Study design Years follow-up Population age and BMI Country	Outcome measure Results at 1 year Results overall (if follow-up > 1 year)	Strengths	Weaknesses	Risk of bias Generalizability
Bahamondes (2001)	Retrospective cohort (n=206) Follow-up: 5 years Ages: Mean 33.1 years +/- 0.7 Baseline BMI: Excluded obese Country: Brazil	Outcome measure: Difference in weight change from baseline between groups Results at 1 year: No statistically significant difference in weight gain between DMPA users and Cu-IUD users (p=0.07). Results overall: DMPA users gained 4.3 kg over 5 years, compared to matched Cu-IUD users who gained 1.8 kg over 5 years (p=0.009). Weight was statistically significantly higher in the DMPA group in years 2-5 of follow-up (p=0.02 at years 2, 3, and 4).	Participants were matched on age and weight	Only those who had used their contraceptive method continuously for 5 years were included. May underestimate weight gain Did not control for physical activity or diet	Risk of bias: High Generalizability: Fair
Batista (2016)	Prospective cohort (n=37) Follow-up: 1 year Ages: Mean 29 years +/- 6 Baseline BMI: Likely no obese-BMI participants Country: Brazil	Outcome measure: Difference in weight change from baseline between groups Results at 1 year: DMPA users and Cu-IUD users had similar mean weight at baseline (62 kg vs 61 kg, respectively, p=0.5449), but the groups had a statistically significant difference in mean weight at one-year follow-up (DMPA 65 kg vs. Cu-IUD 62 kg, p=0.0007). Results overall: As above	Controlled for physical activity by restricting those who exercised. Matched on age and baseline BMI.	Loss to follow-up of 24% Did not control for diet	Risk of bias: Moderate Generalizability: Fair
Berenson (2008)	Prospective cohort (n=608) Follow-up: 2 years Ages: 16-33 years Baseline BMI: All categories included* Country: United States *Ascertained from Berenson & Rahman (2009), which studied the same cohort sample	Outcome measure: % participants reporting weight gain in a symptom checklist Results at 1 year: Not reported Results overall: At 2 years, DMPA users had 2.27 (95% CI 1.73-2.99) times the adjusted odds of reporting weight gain compared to non-hormonal method users, whereas COC users had 1.19 (95% CI 0.90-1.57) times the adjusted odds of reporting weight gain compared to NH users.	Analysis adjusted for follow-up visit, age, race, baseline status of weight gain.	Loss to follow-up or discontinuation: 37-40% at 1 year and 55-61% at 2 years; results at 1 year were not reported Recall bias Weight gain patient-reported DMPA users who reported weight gain at the 6 months were more likely to be lost to follow-up at next visit compared to those who did not report weight gain at 6 months. May underestimate incidence of weight gain	Risk of bias: High Generalizability: Good
Berenson & Rahman (2009)	Prospective cohort (n=703) Follow-up: 3 years Ages: 16-33 years Baseline BMI: All categories included Country: United States	Outcome measure: Differences in weight change and body composition from baseline between groups Results at 1 year: Higher protein intake was protective against gains in body weight and body fat in DMPA and COC users.	Analysis adjusted for diet and physical activity level. Analysis considered age,	Loss to follow-up or discontinuation: 72% Loss to follow-up greater at 6 months in those who had gained >5% total body weight vs. those who had gained <5% total body weight (loss 32.6% vs 12.5%, respectively, p=0.003)	Risk of bias: High Generalizability: Good

		Results overall: Mean weight gain at 3 years was 5.1 kg for DMPA users, 1.5 kg for COC users, and 2.1 kg for NH users (p<0.01 for DMPA compared to COC and NH). DMPA users gained 4.4 kg in the first 18 months and 0.7 kg in the next 18 months. At 3 years, body fat increased 3.4% in DMPA users, 1.6% in COC users, and 0.5% in NH users, and central-to-peripheral fat ratio increased 0.1 units in DMPA users versus 0.0 units in COC and NH users (p<0.01 for all statistics of DMPA compared to COC and NH for body).	age at menarche, parity, previous use of method, income, education, marital status, prior breastfeeding, baseline obesity, and appetite change.	Only 24% of DMPA users were still using DMPA at 3 years. May underestimate weight gain	
Bonny (2009)	Prospective cohort (n=51) Follow-up: Half year Ages: 12-18 years Baseline BMI: Likely no obese-BMI participants Country: United States	Outcome measure: Difference in change in body fat % and lean body mass % from baseline between groups; body composition measured by DEXA Results at 1 year: Not applicable Results overall: At 6 months, total body fat had increased 10.3% in DMPA (with estradiol-placebo) users, decreased 0.1% in COC users, and decreased 0.7% in NH users (p=0.04 for DMPA with placebo vs NH users; no statistically significant difference between DMPA and COC users). Differences in lean body mass changes were not statistically significant.	Analysis considered caloric intake, age, gynecologic age, race, weight height, BMI, baseline total body fat and baseline lean body mass	Did not control for physical activity Small n (i.e., there were only 8 participants in the DMPA with placebo group)	Risk of bias: Moderate Generalizability: Fair
Clark (2005)	Prospective cohort (n=323) Follow-up: 2.5 years Ages: 18-35 years Baseline BMI: Likely no obese-BMI participants Country: United States	Outcome measure: Difference in weight change and body composition from baseline between groups Results at 1 year: DMPA users gained 4 kg weight vs no weight gain in NH users (approximated from graph) Results overall: DMPA users gained 6.1 kg weight, all of which was fat mass. NH users gained "virtually no weight" or fat mass. DMPA users had an increase in ratio of central to peripheral fat mass, while this was unchanged in NH users. No change in lean mass in either group. P<0.03 for all measures. Length of time of DMPA use was strongest predictor of change in weight, fat mass, and central-to-peripheral fat mass ratio. Physical activity associated with less increase in fat mass and fat ratio but not weight.	Analysis adjusted for physical activity level. Covariates considered in analysis: age, age at menarche, number of pregnancies, previous method use, smoking status.	Loss to follow-up 21-22% Did not control for diet	Risk of bias: Moderate Generalizability: Fair
Dal'Ava (2014)	Prospective cohort (n=97) Follow-up: 1 year Ages: 18-50 years Baseline BMI: All categories included Country: Brazil	Outcome measure: Differences in weight change and body composition from baseline between groups Results at 1 year: DMPA users gained mean 1.9 kg (1.6 kg of which was fat mass), while Cu-IUD users gained 1.1 kg (p=0.38). There was no statistically significant difference between groups in variation from baseline of fat mass, lean mass, or peripheral fat %. DMPA users had a 4.6% increase in central fat while Cu-IUD users had a	Participants matched for age and baseline weight	Loss to follow-up or discontinuations: 53% in DMPA users and 38% in Cu-IUD users Measured physical activity (greater in Cu-IUD users) but unable to adjust for it in analysis.	Risk of bias: High Generalizability: Fair

		3.7% decrease in central fat from baseline (difference between groups p=0.04). Results overall: As above			
Dos Santos (2014)	Prospective cohort (n=40) Follow-up: 1 year Ages: 18-40 years Baseline BMI: Excluded obese Country: Brazil	Outcome measure: Differences in weight change and body composition from baseline between groups Results at 1 year: DMPA users gained 1.4 kg +/- standard error 0.7 and Cu-IUD users gained 0.3 kg +/- 0.5 (p=0.18). DMPA users had a 2% +/- 0.9 increase in body fat and 2% +/- 0.9 decrease in lean mass from baseline, while Cu-IUD users had a 0.7% +/- 0.7 increase in body fat and 0.7% +/- 0.7 decrease in lean mass (difference between groups not statistically significant, p=0.20 for all measures). Results overall: As above	Participants were matched by age and weight All participants encouraged to adopt healthy habits No loss to follow-up	Physical activity data collected but not incorporated into analysis	Risk of bias: Moderate Generalizability: Fair
Dos Santos (2016)	Prospective cohort (n=53) Follow-up: 1 year Ages: 18-40 years Baseline BMI: Excluded obese Country: Brazil *Included some participants from Dos Santos 2014	Outcome measure: Differences in BMI, binge eating behavior, and appetite stimulation seromarkers from baseline between groups Results at 1 year: DMPA users vs Cu-IUD users who were paired at baseline by age and BMI had no statistically significant differences in change of BMI, Binge Eating Scale scores, or in seromarkers of central appetite stimulation (as measured by neuropeptide Y, leptin, and adiponectin). BMI increased by mean of 0.8 kg/m^2 in DMPA users and decreased by mean 0.2 kg/m^2 in Cu-IUD users (p=0.87). Results overall: As above	Matched for age and BMI at baseline. Level of activity similar at baseline. Diet (frequency and quantity of eating) was part of outcome measure in Binge Eating Scale.	Loss to follow-up 7-31% With small sample size, large variation in BMI within groups caused high p-value despite point estimates appearing different.	Risk of bias: Moderate Generalizability: Fair
Espey (2000)	Retrospective cohort (n=306) Follow-up: 2 years Ages: 18-40 years Baseline BMI: All categories included Country: United States (specifically Navajo population at Indian Health Service sites)	Outcome measure: Differences in weight change from baseline between groups Results at 1 year: DMPA users gained 4.2 kg while non-DMPA users gained 1.4 kg (p<0.001). Results overall: DMPA users gained 7.2 kg while non-DMPA users gained 1.8 kg (p<0.001).	Covariates considered: age, parity, baseline weight	Participants were included only if they had used method for 5 consecutive injections (i.e., for greater than 1 consecutive year). This may underestimate actual weight gain, as those who had unacceptable side effects may have discontinued method and been excluded from study.	Risk of bias: High Generalizability: Fair
Modesto (2014)	Retrospective cohort (n=2138) Follow-up: 10 years Ages: 18-40 years Baseline BMI: Likely no obese-BMI participants Country: Brazil	Outcome measure: Difference in weight change from baseline between groups Results at 1 year: Weight gain by method: DMPA 1.3 kg, LNG-IUS 0.7 kg, Cu-IUD 0.2 kg, statistically significant for DMPA vs Cu-IUD (p<0.0001) and DMPA vs LNG-IUS (p=0.02) but not for Cu-IUD vs LNG-IUS (p=0.17). Results overall: Weight gain by method: DMPA 6.6 kg, LNG-IUS 4.0 kg, Cu-IUD 4.9 kg, statistically significant for DMPA vs Cu-IUD (p=0.04) and DMPA vs LNG-IUS	Term "Retrospective cohort" strictly applied; study designed more like prospective cohort. Adjusted for years of schooling and	Loss to follow-up or discontinuation at 1 year: 5-17% Loss to follow-up or discontinuation at 10 years: 79-90% DMPA users had mean baseline weight 7.8kg lower than LNG-IUS users. Analysis did not adjust for baseline weight. Did not control for diet or physical activity	Risk of bias: Moderate Generalizability: Fair

		(p=0.02) but not for Cu-IUD vs LNG-IUS (p=0.35). P-values are adjusted.	number of children.		
Nault (2013)	Prospective cohort (n=4133) Follow-up: 1 year Ages: 14-45 years Baseline BMI: All categories included Country: United States	Outcome measure: % participants reporting weight gain Results at 1 year: Relative to Cu-IUD users, DMPA users had adjusted (for race) relative risk 1.37 (95% CI 1.14-1.64) for perceived weight gain and implant users had adjusted relative risk 1.29 (95% CI 1.10-1.51). LNG-IUS, pill, patch, ring users were no more likely to perceive weight gain compared to Cu-IUD. The sensitivity of perceived weight gain was 74.6%, specificity was 84.4%, and positive predictive value was 77%. Results overall: As above	Covariates considered in analysis: race, socioeconomic status, baseline BMI	Poor measurement of perceived weight gain (e.g., at each interval, participants were asked if they had perceived a weight change of 5 lbs or more and if participants perceived weight change of less than 5 lbs, it would be recorded as no perceived weight change)	Risk of bias: High Generalizability: Good
Pantoja (2010)	Retrospective cohort (n=758) Follow-up: 3 years Ages: Reproductive years (mean age 30.8 +/- 6.8 years) Baseline BMI: All categories included Country: Brazil	Outcome measure: Difference in weight change between study groups, stratified by BMI category Results at 1 year: Not reported Results overall: In the normal-weight stratum, DMPA users gained mean 4.5 kg +/- standard deviation 4.5 while Cu-IUD users gained 1.2 kg +/- 4.0 (p=0.0107). In the overweight stratum, DMPA users gained mean 3.4 kg +/- 5.5 while Cu-IUD users gained 0.2 +/- 4.9 (p<0.0001). Weight gain was not statistically different between DMPA and Cu-IUD users in the obese-weight stratum.	Paired for age and baseline BMI	Sample was women who had already been using contraceptive method for 3 years, so those who discontinued method sooner for possible negative side effects were excluded May underestimate actual weight gain	Risk of bias: High Generalizability: Fair
Taneepanichskul (1998, 1999)	Retrospective cohort (n=100) Follow-up: 10 years Ages: 37-50 years Baseline BMI: Likely no obese-BMI participants Country: Thailand	Outcome measure: Difference in weight change between study groups Results at 1 year: Not reported Results overall: DMPA users and Cu-IUD users both gained approximately 10 kg over the 10 years of follow-up. There was no statistically significant difference in the mean weight between groups at baseline, at 5 years, or at 10 years.	Participants were matched at baseline for age, parity, income, and weight.	Sample was women who had already been using contraceptive method for 10 years, so those who discontinued method sooner for possible negative side effects were excluded. May underestimate actual weight gain	Risk of bias: High Generalizability: Fair
Vickery (2013)	Prospective cohort (n=427) Follow-up: 1 year Ages: 14-45 years Baseline BMI: All categories included Country: United States	Outcome measure: Difference in weight change from baseline between groups Results at 1 year: Weight gain was as follows: Implant users 2.1 kg +/- standard deviation 6.7; LNG-IUS users 1.0 kg +/- 5.3; DMPA users 2.2 kg +/- 4.9, and Cu-IUD users 0.2 kg +/- 5.1. There was no statistically significant difference in weight gain between groups when adjusted for age and race. Black race was a predictor of weight gain regardless of contraceptive method use and age. Results overall: As above	Adjusted for age and race	Large variability in weight gain within groups decreased the power to detect differences between groups Did not control for diet or physical activity Samples was women who had already been using method for 11 months.	Risk of bias: High Generalizability: Good

Appendix 7. Study Characteristics for References Reporting on Mood, Sexual Interest, and Libido

Author (Year)	Study design Years follow-up Population age and BMI Country	Outcome measure Results at 1 year Results overall (if follow-up > 1 year)	Strengths	Weaknesses	Risk of bias Generalizability
Berenson (2008)	Prospective cohort (n=608) Follow-up: 2 years Ages: 16-33 years Country: United States	Outcome measure: % participants reporting nervousness, depressive symptoms, mood swings, loss of libido, using standardized behavioral measures Results at 1 year: Not reported Results overall: At 2 years, DMPA users compared to NH users had greater odds of loss of libido, aOR 2.24 (95% CI 1.50-3.34). DMPA users compared to NH users had a lower odds of mood swings, aOR 0.66 (95% CI 0.45-0.97). There was equivalence for nervousness, and depressive symptoms.	Analysis adjusted for follow-up visit, age, race, baseline status of symptoms.	Loss to follow-up or discontinuation: 37-40% at 1 year and 55-61% at 2 years; results at 1 year were not reported Recall bias Did not account for potential confounders: relationship status and satisfaction or socioeconomic instability	Risk of bias: High Generalizability: Good
Brown (2008)	Prospective cohort (n=36) Follow-up: 0.25 years Ages: 18-36 years Country: United States	Outcome measure: Differences in well-being, sleep, and exercise patterns between groups, as measured by daily questionnaires with a 1-3 scoring system and pedometer readings Results at 1 year: Not applicable Results overall: DMPA or COC users reported more overall negative well-being than NH users in the investigator-designed scoring system based on DSM-IV criteria for Premenstrual Dysphoric Disorder (p=0.038, composite point estimates not reported). Positive well-being at mid-cycle was correlated with more sleep in the COC and NH groups but not in the DMPA group.	Adjusted for age. Other variables considered: % body fat, BMI, university attendance, ethnicity, diet.	Measurement instrument not validated Did not account for potential confounders: relationship status or satisfaction, life stressors, financial instability.	Risk of bias: High Generalizability: Good
Boozalis (2016)	Cross-sectional (n=1,938)* Follow-up: Half year Ages: 14-45 years Country: United States *Included a subgroup analysis of a 6-month prospective cohort (n=560)	Outcome measure: Difference in sexual desire between groups, as answered yes/no to whether they lacked interested in having sex for several months during the last 6 months, asked at 6 months since method initiation (and asked at baseline for a subgroup of participants) Results at 1 year: Not applicable Results overall: At 6 months of use, 18% of Cu-IUD users reported lack of interest in having sex vs 36% of DPMA, 22% of hormonal IUD, 22% of implant, 25% of COC, 33% of patch, and 23% of ring users. In cross-sectional study, adjusted odds ratio for lack of sexual desire in DMPA users vs Cu-IUD users was 2.61, 95% CI 1.47-4.61. In the subgroup cohort where they were able to adjust for baseline sexual desire, adjusted odds ratio was 1.99 (95% CI 0.79-5.05). Lack of interest in having sex at baseline was strongly associated with lack of interest in having sex at 6 months (adjusted OR 3.98; 95% CI 2.58-6.14).	Variables included in multivariable logistic regression: sex, race, parity, receiving public assistance, and contraceptive method. Subgroup cohort analysis included baseline lack of interest in having sex. Other variables	Did not account for potential confounder: relationship satisfaction	Risk of bias: Moderate Generalizability: Good

			considered: marital status or cohabitation, comorbidities, etc.		
Civic (2000)	Prospective cohort (n=457) Follow-up: 3 years Ages: 18-39 years Country: United States	Outcome measure: Difference in depressive symptoms from baseline between groups, as measured by the 10-item Community Epidemiology Survey—Depression Scale (CES-DS) Results at 1 year: Not applicable Results overall: At 3 years, users of DMPA had adjusted odds ratio 1.44 compared to non-users of DMPA for depressive symptoms of 10 or more points on the CES-DS (p=0.047; 95% CI 1.00-2.07). DMPA discontinuers had 1.60 times the adjusted odds compared to non-users of DMPA (p=0.036; 95% CI 1.03-2.48).	Adjusted for race, education, age, and prior history of depression	Loss to follow-up or discontinuation: 60% Did not account for potential confounders: relationship status and satisfaction or socioeconomic instability	Risk of bias: High Generalizability: Good
Ott (2008)	Prospective cohort (n=328) Follow-up: Up to 3.4 years Ages: 14-17 years Country: United States	Outcome measure: Differences in mood and sexual interest between groups over time, as measured by an investigator-designed scoring system of interviews and diary entries Results at 1 year: Not applicable Results overall: On a 3-item scale with range of scores 3-15, DMPA users scored 9.18 for positive mood while stable COC users scored 9.55 (p<0.01 compared to DMPA) and non-DMPA/non-COC users scored 9.16 (p = non-significant). On the same scale, DMPA users scored 5.79 for negative mood while stable COC users scored 5.38 (p<0.001) and non-DMPA non-COC users scored 5.60 (p<0.05). There was no statistical significance in sexual interest between groups.	Adjusted for age	Did not account for potential confounders: relationship status or satisfaction, socioeconomic instability Measurement instrument not validated Authors did not pre-define what difference in score would indicate clinical significance	Risk of bias: High Generalizability: Good
Schaffir (2010)	Cross-sectional (n=50) Follow-up: 0 years Ages: 18+ Country: United States	Outcome measure: Difference in sexual desire and function between groups, as measured by the Female Sexual Function Index questionnaire Results at 1 year: Not applicable Results overall: Between DMPA users and COC users, scores of desire (4.2 vs 3.8, p=0.27), arousal (5.0 vs 4.8, p=0.46), and total scores (30.1 vs 28.8, p=0.28) were no different. COC users scored higher on the satisfaction domain, which solicits satisfaction with the emotional and sexual aspects of the relationship (5.4 vs 4.8, p=0.02).	Variables considered: satisfaction with contraception, satisfaction with relationship, and level of life stress. Controlled for ethnicity, education, gravidity, monthly bleeding, and frequency of intercourse.	Participants had already been using their contraceptive method for an average of 4-5 years without an interest in changing it. This sampling may overestimate sexual function, as those with undesirably decreased sexual function may have discontinued the method earlier and not been recruited to the study.	Risk of bias: High Generalizability: Good

Appendix 8. Study Characteristics for References Reporting on Other Side Effects and Health Benefits

Author (Year)	Study design Years follow-up Population age and BMI Country	Outcome measure Results at 1 year Results overall (if follow-up > 1 year)	Strengths	Weaknesses	Risk of bias Generalizability
Bahamondes (1994)	Case-control (n=645) Follow-up: N/A Ages: Mean 28.5 years at time of diagnosis Country: Brazil	Outcome measure: Risk of infertility due to tubal obstruction Results at 1 year: Not applicable Results overall: Past-DMPA users had lower odds of infertility caused by tubal obstruction compared to never-DMPA users, aOR 0.35 (95% CI 0.1-0.8). Barrier contraceptive users and COC users had even lower odds (aOR 0.16 with 95% CI 0.1-0.5, aOR 0.27 with 95% CI 0.2-0.3, respectively) compared to never-barrier users and never-COC users. When considering only those with secondary infertility, the protective effects of DMPA were eliminated while protective effects of COCs persisted.	Cases and controls were matched on age at diagnosis and level of education. Cases and controls selected from same hospital and had similar socioeconomic status.	Recall bias	Risk of bias: Moderate Generalizability: Fair
Berenson (2008)	Prospective cohort (n=608) Follow-up: 2 years Ages: 16-33 years Country: United States	Outcome measure: % participants reporting menstrual and other side effects, using a symptom checklist Results at 1 year: Not reported Results overall: At 2 years, DMPA users compared to NH users had greater odds of reporting continuous bleeding longer than 20 days (adjusted odds ratio 13.37, 95% CI 5.35-33.38), intermenstrual bleeding (aOR 3.61, 95% CI 2.22-5.90), missed periods (aOR 96.90, 95% CI 53.81-174.47), and loss of energy (aOR 1.55, 95% CI 1.10-2.18). Compared to NH users, DMPA users had lower odds of bloating (aOR 0.48, 95% CI 0.34-0.69) and cramping (aOR 0.35, 95% CI 0.24-0.51) but similar odds of mastalgia, acne, scalp hair loss, hirsutism, dyspareunia, and headache.	Analysis adjusted for follow-up visit, age, race, baseline status of symptoms.	Loss to follow-up or discontinuation: 37-40% at 1 year and 55-61% at 2 years; results at 1 year were not reported Recall bias DMPA users who reported bleeding longer than 20 days at 1 year were more likely to switch their method at the following visit. DMPA users who reported bloating at 1.5 years were more likely to switch their method at the following visit. May underestimate incidence of symptoms	Risk of bias: High Generalizability: Good
Cuevas (1991)	Case-control (n=2005) Follow-up: N/A Ages: Mean 41.3 years at time of diagnosis Country: Mexico, Thailand	Outcome measure: Risk of histologically confirmed epithelial ovarian cancer Results at 1 year: Not applicable Results overall: Adjusted relative risk of epithelial ovarian cancer in ever-DMPA users vs never-users was 1.07 (95% CI 0.6-1.8). The risk of epithelial ovarian cancer was not	Cases and controls were matched on age, hospital, and year of interview. Controlled for confounders of	Risk of recall bias	Risk of bias: Moderate Generalizability: Fair

		altered by use of DMPA, nor by duration of DMPA use, time since first or most recent use, or age at first use of DMPA.	parity and COC use. Many other medical and social variables were considered.		
Silpisornkosol (1991)	Case-control (n=1061) Follow-up: N/A Ages: Mean 48 years at diagnosis Country: Thailand	Outcome measure: Risk of histologically confirmed endometrial cancer Results at 1 year: Not applicable Results overall: Adjusted relative risk of endometrial cancer was estimated to be 0.21 (95% CI 0.06-0.79) in ever-users of DMPA compared to never-users (excluding those who had first used DMPA in the year prior to diagnosis, likely prescribed for symptoms related to endometrial cancer).	Cases and controls were matched on age, hospital, and year of interview. Many other medical and social variables were considered.	Risk of recall bias Did not account for confounding or mediation of obesity, which is a known risk factor for endometrial cancer.	Risk of bias: High Generalizability: Fair
Wilailak (2012)	Case-control (n=1312) Follow-up: N/A Ages: 20-70 years Baseline BMI: 23 to 24 +/- 4 years Country: Thailand	Outcome measure: Risk of histologically confirmed epithelial ovarian cancer Results at 1 year: Not applicable Results overall: Ever-users of DMPA had adjusted odds ratio of 0.61 (p<0.001; 95% CI 0.44-0.85) for ovarian cancer compared to never-users. Odds of ovarian cancer were even lower compared to never-users when duration of DMPA use was >3 years (aOR 0.17; p<0.001; 95% CI 0.07-0.39).	Cases and controls were matched on age, hospital, and year of interview. Many other medical and social variables were considered.	Risk of recall bias	Risk of bias: Moderate Generalizability: Fair
Ziaei (2004)	Prospective cohort (n=400) Follow-up: 0.25 years Ages: 18-42 years: Country: Iran	Outcome measure: Differences in urological symptoms and urinary tract infections between groups Results at 1 year: Not applicable Results overall: Comparing DMPA users to withdrawal method users, incidence of urinary tract infection was 5% vs 0.5%, respectively (p=0.018). There were also statistically significant differences in urinary frequency and urinary incontinence between groups (p<0.001).	Participants were matched on age, gravidity, socioeconomic and educational status	Did not account for potential confounding or mediation of frequency of sexual activity	Risk of bias: Moderate Generalizability: Fair

