

妇癌专题

• 临床研究 •

子宫肌瘤患者血清性激素水平的 Meta 分析*

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[摘要] 目的: 系统评价子宫肌瘤患者与非子宫肌瘤患者血清雌激素、孕激素、卵泡刺激素(FSH)、黄体生成素(LH)水平的差异, 为子宫肌瘤的发病风险评估及临床诊治提供依据。方法: 计算机检索 1995 年至今在 Pubmed、CNKI、万方、维普等数据库公开发表的相关文献, 根据 Newcastle-Ottawa Scale (NOS) 量表对入选文献进行质量评价, 采用 RevMan 5.3 软件绘制森林图, Stata 12.0 软件进行敏感性分析和发表偏倚评估。结果: 共纳入 17 篇研究, 累计子宫肌瘤患者 1 549 例, 对照组 863 例, 计算合并 SMD 及其 95% CI, Meta 分析结果显示, 子宫肌瘤患者卵泡期血清 FSH (SMD = 0.34, 95% CI: 0.10 ~ 0.59, P = 0.006)、LH (SMD = 0.40, 95% CI: 0.24 ~ 0.55, P < 0.001) 水平高于对照组, 而卵泡期血清雌激素、孕激素及黄体期血清雌激素、孕激素、FSH、LH 水平与对照组相比, 差异无统计学意义。结论: 卵泡期血清 FSH、LH 水平较高的女性有更高的子宫肌瘤发病风险, 卵泡期血清雌激素、孕激素和黄体期血清雌激素、孕激素、FSH、LH 水平与子宫肌瘤的发生无显著联系。

[关键词] 子宫肌瘤; 性激素; 雌激素; 孕激素; 卵泡刺激素; 黄体生成素; Meta 分析

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A Meta Analysis of Serum Sex Hormone in Patients with Uterine Fibroids

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[Abstract] **Objective:** To systematically evaluate the differences in serum estrogen, progesterone, follicular stimulating hormone (FSH) and luteinizing hormone (LH) between patients with uterine fibroids and those without uterine fibroids, providing a basis for risk assessment, clinical diagnosis and treatment of uterine fibroids. **Methods:** Relevant articles published in Pubmed, CNKI, Wanfang and VIP databases since 1995 were searched by computer. Quality of the selected articles was evaluated according to the Newcastle-Ottawa Scale. RevMan 5.3 was used to draw forest plots, and Stata 12.0 was used for influence analysis and publication bias evaluation. **Results:** Seventeen studies, comprising 1,549 cases of uterine fibroids and 863 cases in control group, were included. SMD and 95% CI were calculated. The results showed that serum FSH (SMD

0.34, 95% CI: 0.10 ~ 0.59, P = 0.006) and LH (SMD = 0.40, 95% CI: 0.24 ~ 0.55, P < 0.001) in patients with uterine fibroids in follicular phase were higher than those in the control group, and that there were no statistically significant differences between the two groups in serum estrogen and progesterone in follicular phase and serum estrogen, progester-

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one, FSH and LH in luteal phase. **Conclusion:** Women with higher serum FSH and LH during follicular phase risk higher incidence of uterine fibroids. The incidence of uterine fibroids is not correlated to serum estrogen and progesterone in follicular phase and serum estrogen, progesterone, FSH and LH in luteal phase.

[**Key words**] Uterine fibroids; Sex hormone; Estrogen; Progesterone; Follicle stimulating hormone (FSH); Luteinizing hormone (LH); Meta-analysis

子宫肌瘤(uterine fibroid)是起源于子宫平滑肌细胞的良性肿瘤,多发生于育龄期女性,发病率为 20%~40%,青春期少见,妊娠期有增大风险,绝经后多萎缩退化^[1-2],可导致不规则子宫出血、盆腔疼痛、不孕、反复流产及尿频、便秘等症状^[3-5]。据报道,全球范围内因子宫肌瘤行子宫切除的病例占子宫切除术总数的 1/3~1/2,医疗费用支出较大^[6]。

近年来,大量研究表明肌瘤的发生与子宫肌层局部雌孕激素水平的升高及其相关受体的增加有关^[7-8],但迄今为止,子宫肌瘤的发病机制尚不明确,并且缺乏有效的保守治疗方法^[9-11]。子宫肌瘤患者血清雌激素、孕激素、FSH、LH 水平变化的相关报道不一致,且存在争议^[12-15]。为进一步探讨子宫肌瘤患者与非子宫肌瘤人群血清性激素水平是否存在差异,评估血清性激素水平与子宫肌瘤发病风险的相关性,为其发生、预防提供循证医学依据,本文采用 Meta 分析的方法,利用已发表的相关研究,对子宫肌瘤患者血清性激素水平进行系统评价。

1 资料与方法

1.1 资料来源

检索中国知网、维普、万方、Pubmed 等数据库。中文检索词包括:子宫肌瘤、血清性激素、血清雌激素、血清孕激素、血清卵泡刺激素、血清黄体生成素等。英文检索词包括:leiomyoma of uterus、uterine myoma、uterine fibroid、serum sex hormone、serum gonadal hormone、serum estrogen、serum progesterone、serum follicle stimulating hormone (FSH)、serum luteinizing hormone (LH)。检索日期为 1995 年至今。以 Pubmed 为例,具体检索策略见图 1。

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#1 uterine fibroid OR uterine myoma OR leiomyoma of uterus
#2 serum sex hormone OR serum gonadal hormone OR serum estrogen
OR serum progesterone OR serum follicle stimulating hormone OR serum luteinizing hormone
#3 #1 AND #2
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图 1 PubMed 检索策略

Figure 1. Searching Strategy for Pubmed

1.2 文献纳入和排除标准

纳入标准:①原始文献为病例对照研究;②病理

及影像学确诊为子宫肌瘤;③资料完整,有明确的研究设计、样本含量及均数±标准差($\bar{x} \pm s$);④病例组和对照组均无影响体内激素水平的其他病理生理因素,近 3 个月内未使用激素类及影响激素水平的药物,近期无人工流产及哺乳史,且月经规律;⑤组间年龄差异无统计学意义;⑥检测方法相似,均为静脉血标本。排除标准:①样本来源不符合纳入标准,文献质量差;②未测定激素水平,或已测定但未说明测定时期的文献;③原始资料未设立对照组、综述或个案报道;④重复报告、发表的文献。

1.3 资料提取

由两名研究者独立提取、分析资料,如遇分歧,相互讨论或由第三名研究者协助解决。资料提取信息包括:题目、作者、年份、期刊、样本量、年龄、诊断标准、采血时间、激素水平检测方法 & 检测结果等。

1.4 质量评价

根据 Newcastle-Ottawa Scale (NOS) 量表针对病例对照研究制定的标准评价纳入文献质量。包括 3 个栏目(研究人群选择、组间可比性、暴露因素测量),8 个给分条目,9 个给分点,合计评分大于 6 分认为是高质量文献^[16]。

1.5 统计分析

按 Meta 分析的要求整理及建立数据库,采用 RevMan 5.3 软件进行分析。异质性以 I^2 统计量进行评估,若 $I^2 \geq 50\%$,认为存在异质性,采用随机效应模型;若 $I^2 < 50\%$ 说明纳入研究同质,采用固定效应模型。以标准化均数差 SMD、95% CI 及 P 值作为合并效应统计量, $P < 0.05$ 认为差异有统计学意义。采用 Stata 12.0 软件进行敏感性分析和通过 Egger's 检验评价发表偏倚。血清雌激素水平采用的计量单位为 pg/mL,孕激素为 ng/mL,FSH、LH 为 IU/L。各激素水平计量单位转换标准:雌激素为 1pmol/L = 3.67pg/mL,1pg/mL = 1ng/L;孕激素为 1nmol/L = 3.18ng/mL,1ng/mL = 1ug/L;FSH、LH 为 1IU/L = 1mIU/mL。

2 结果

2.1 文献检索结果

初筛文献 1 791 篇,排除重复文献,阅读题目和

摘要后,初步纳入 227 篇,通过阅读全文后最终纳入 17 篇。其中研究雌激素水平的文献(卵泡期 14 篇,黄体期 7 篇)有 14 篇,孕激素水平的文献(卵泡期

12 篇,黄体期 7 篇)有 12 篇,FSH 水平的文献(卵泡期 12 篇,黄体期 7 篇)有 12 篇,LH 水平的文献(卵泡期 10 篇,黄体期 6 篇)有 10 篇(图 2)。

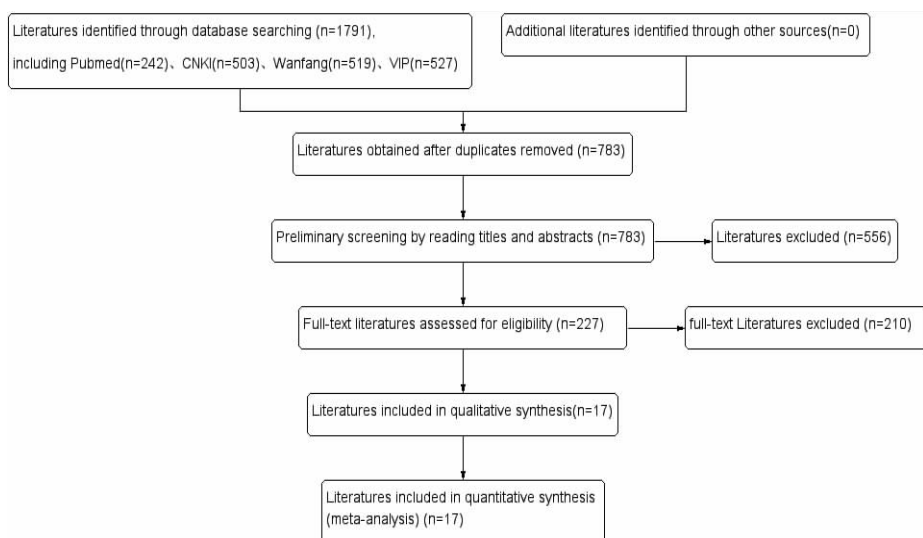


图 2 文献筛选流程

Figure 2. Flow of Article Screening

2.2 纳入研究及其方法学质量评价

其中英文文献 4 篇,中文文献 13 篇,纳入文献基本特征及质量评价结果见表 1。累计子宫肌瘤病

例 1 549 例,对照组 863 例,各研究因素纳入文献汇总见表 2。

表 1 纳入文献基本特征及质量评价

Table 1. Basic Characteristics and Quality Assessment of Included Articles

Study	Average age (UL/C, y)	Time of blood collection (UL/C)	Detection method	Characteristics of leiomyoma			Quality assessment of NOS
				Location	Number	Diameter (mm)	
Basta P ^[17] 2009	-/-	Be/Be	-	-	-	-	7
Dingiloglu BS ^[18] 2007	45.8/44.1	-/-	-	-	-	-	7
Paffoni A ^[19] 2013	37.8/37.8	-/-	-	Intramural, submucosal, subserosal	Single, multiple	2.2 ± 1.2	7
Richlin SS ^[20] 2002	34.9/34.9	-/-	CLIA	Intramural, submucosal	-	-	7
Xu CX ^[21] 2008	46.4/44.8	-/-	-	-	-	-	7
Liu MH ^[22] 2003	39.2/37.4	Be/Be	RIA	-	-	-	7
Chen HL ^[23] 2000	43/-	Be/-	RIA	-	Single, multiple	-	7
Xie YS ^[24] 2014	44/41	Be/Be	CLIA	-	-	-	7
Li XK ^[15] 2012	37.1/36.8	-/-	CLIA	Intramural, subserosal	Single, multiple	-	6
Cao SJ ^[25] 1998	45.1/44.3	Be/Be	RIA	-	-	-	7
Wang XP ^[26] 1998	41.7/37.1	Be/-	RIA	-	-	-	7
Zhang LA ^[12] 2003	-/-	-/-	RIA	-	-	-	7
Ma ZS ^[27] 1997	-/-	Be/Af	RIA	-	Single, multiple	-	7
Huo Y ^[28] 2007	41.6/42.4	-/-	CLIA	-	-	≥2	7
Zhang SG ^[29] 2003	44.4/40.3	-/-	RIA	-	-	-	7
Chen J ^[30] 2000	-/-	Be/Be	RIA	Intramural, submucosal, subserosal	Single, multiple	-	6
Shang LX ^[13] 1995	-/-	Be/Af	RIA	Intramural, submucosal, subserosal	-	1 ~ 10	7

UL: uterine leiomyoma group; C: control group; RIA: radioimmunoassay; CLIA: chemiluminescence immunoassay; Be: before a meal; Af: after a meal; “-”: exclusions or no data.

表 2 各研究因素纳入文献汇总

Table 2. Included Articles of Varied Factors

Study	Follicular phase					Luteal phase				
	Number of samples (UL/C)	Estrogen	Proges-terone	FSH	LH	Number of samples (UL/C)	Estrogen	Proges-terone	FSH	LH
Basta P ^[17] 2009	21/9	included	included	included	-	12/10	included	included	included	-
Dingiloglu BS ^[18] 2007	38/30	included	-	included	included	-	-	-	-	-
Paffoni A ^[19] 2013	128/256	-	-	included	-	-	-	-	-	-
Richlin SS ^[20] 2002	12/20	-	included	-	-	-	-	-	-	-
Xu CX ^[21] 2008	23/52	included	included	included	included	-	-	-	-	-
Liu MH ^[22] 2003	15/18	included	included	included	included	15/12	included	included	included	included
Chen HL ^[23] 2000	24/20	included	-	-	-	-	-	-	-	-
Xie YS ^[24] 2014	142/80	included	-	-	-	-	-	-	-	-
Li XK ^[15] 2012	785/80	included	included	included	included	-	-	-	-	-
Cao SJ ^[25] 1998	31/36	included	included	included	included	36/36	included	included	included	included
Wang XP ^[26] 1998	18/13	included	included	included	included	22/18	included	included	included	included
Zhang LA ^[12] 2003	18/20	included	-	included	included	22/20	included	-	included	included
Ma ZS ^[27] 1997	22/19	included	included	included	included	-	-	-	-	-
Huo Y ^[28] 2007	60/30	included	included	-	-	-	-	-	-	-
Zhang SG ^[29] 2003	21/21	included	included	-	-	20/19	included	included	-	-
Chen J ^[30] 2000	17/14	-	included	included	included	13/10	-	included	included	included
Shang LX ^[13] 1995	13/10	included	included	included	included	21/10	included	included	included	included

UL: uterine leiomyoma group; C: control group; “-”: exclusions or no data.

2.3 Meta 分析结果

2.3.1 卵泡期血清雌激素水平 纳入 14 项研究^[12-13,15,17-18,21-29], 子宫肌瘤组 1 231 例, 对照组 438 例, 各纳入研究间存在异致性 ($I^2 = 76%$), 采用随机

效应模型, 合并效应量结果显示两组卵泡期血清雌激素水平差异无统计学意义 ($SMD = 0.13, 95% CI: -0.14 \sim 0.40, P = 0.35$) (图 3)。

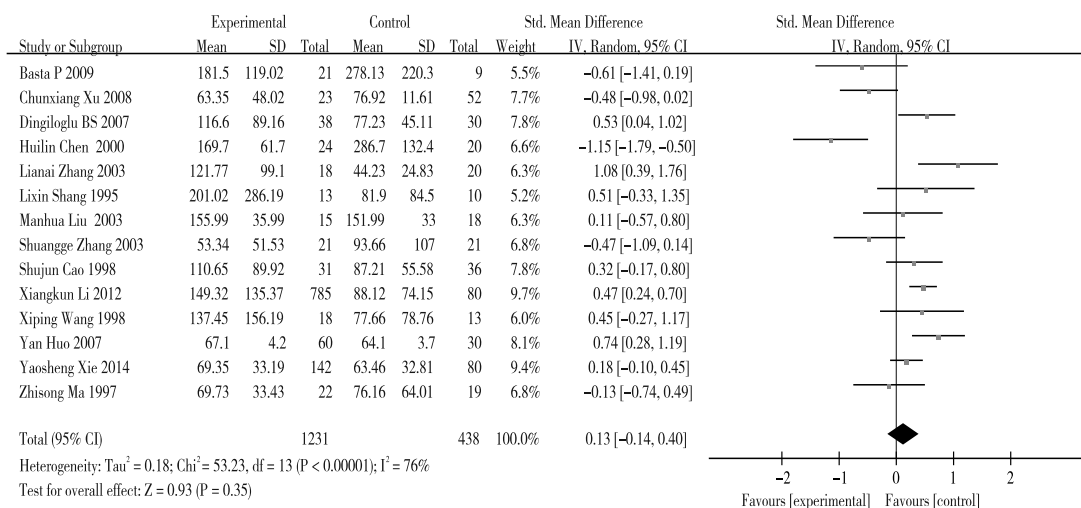


图 3 两组卵泡期血清雌激素水平比较的森林图

Figure 3. Serum Estrogen during Follicular Phase in Two Groups

2.3.2 黄体期血清雌激素水平 7 项研究^[12-13,17,22,25-26,29], 子宫肌瘤组 148 例, 对照组 125 例, 各纳入研究同质 ($I^2 = 46%$), 采用固定效应模

型, 合并效应量结果显示两组黄体期血清雌激素水平差异无统计学意义 ($SMD = 0.03, 95% CI: -0.21 \sim 0.27, P = 0.81$) (图 4)。

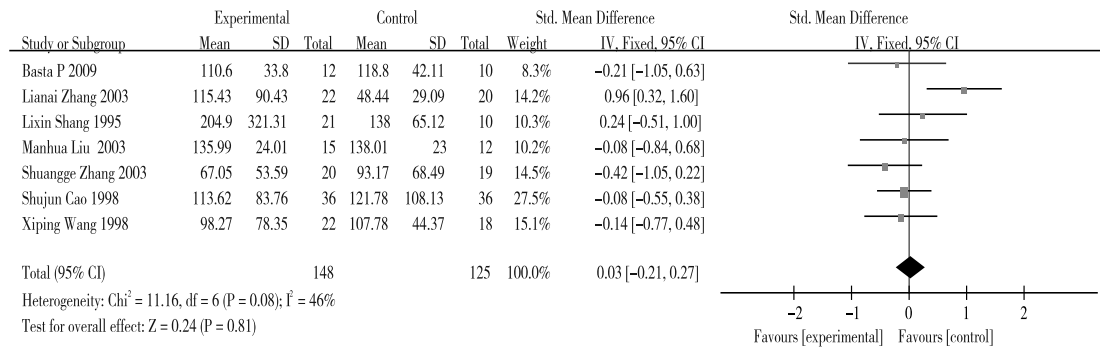


图 4 两组黄体期血清雌激素水平比较的森林图

Figure 4. Serum Estrogen during Luteal Phase in Two Groups

2.3.3 卵泡期血清孕激素水平 12 项研究^[13,15,17,20-22,25-30], 子宫肌瘤组 1 038 例, 对照组 322 例, 各纳入研究间存在异致性 ($I^2 = 78\%$), 采用随机

效应模型, 合并效应量结果显示两组卵泡期血清孕激素水平差异无统计学意义 ($SMD = -0.04$, 95% $CI: -0.38 \sim 0.31$, $P = 0.84$) (图 5)。

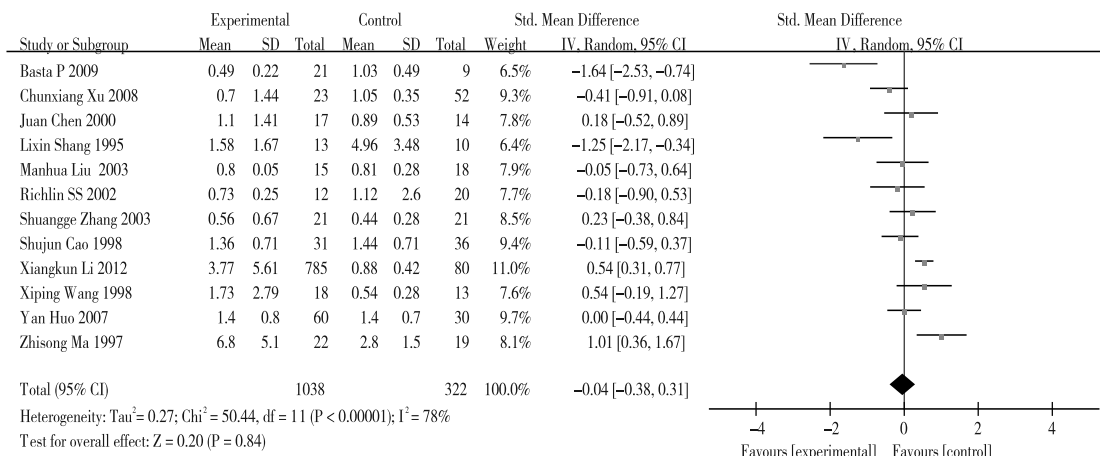


图 5 两组卵泡期血清孕激素水平比较的森林图

Figure 5. Serum Progesterone during Follicular Phase in Two Groups

2.3.4 黄体期血清孕激素水平 7 项研究^[13,17,22,25-26,29-30], 子宫肌瘤组 139 例, 对照组 115 例, 各纳入研究间存在异致性 ($I^2 = 66\%$), 采用随机

效应模型, 合并效应量结果显示两组黄体期血清孕激素水平差异无统计学意义 ($SMD = -0.17$, 95% $CI: -0.62 \sim 0.28$, $P = 0.45$) (图 6)。

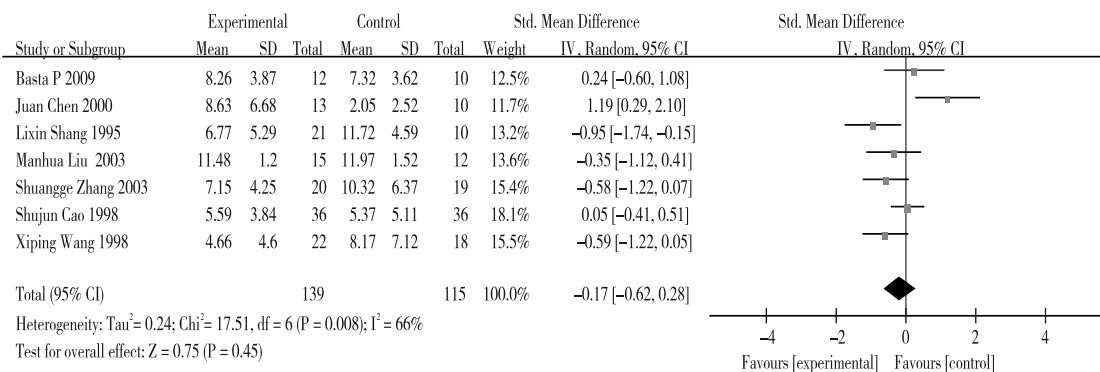


图 6 两组黄体期血清孕激素水平比较的森林图

Figure 6. Serum Progesterone during Luteal Phase in Two Groups

2.3.5 卵泡期血清 FSH 水平 12 项研究^[12-13,15,17-19,21-22,25-27,30], 子宫肌瘤组 1 129 例, 对照组 557 例, 各纳入研究间存在异致性 ($I^2 = 66\%$), 采

用随机效应模型, 合并效应量结果显示子宫肌瘤患者卵泡期血清 FSH 水平高于对照组 ($SMD = 0.34$, 95% $CI: 0.10 \sim 0.59$, $P < 0.01$) (图 7)。

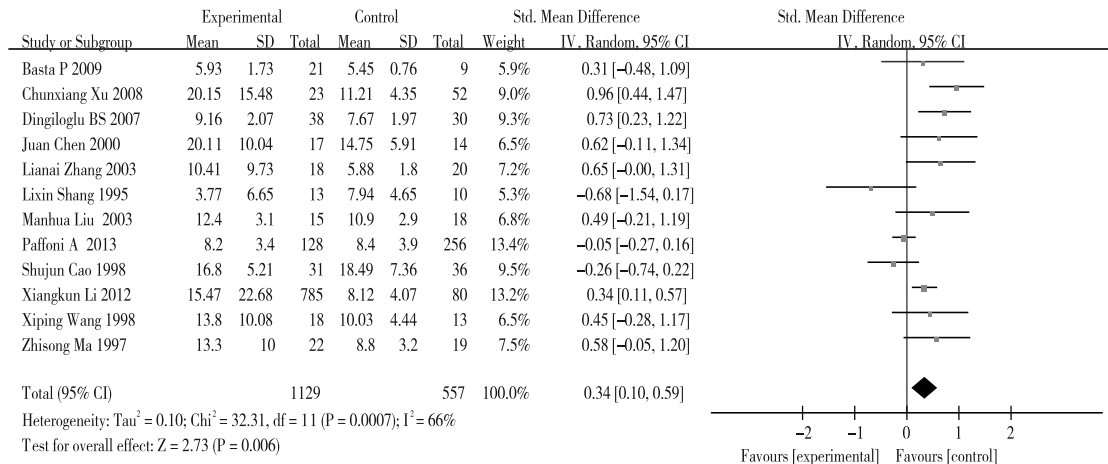


图 7 两组卵泡期血清 FSH 水平比较的森林图
 Figure 7. Serum FSH during Follicular Phase in Two Groups

2.3.6 黄体期血清 FSH 水平 7 项研究^[12-13, 17, 22, 25-26, 30], 其中子宫肌瘤组 141 例, 对照组 116 例, 各纳入研究同质 (I² = 38%), 采用固定效应

模型, 合并效应量结果显示两组黄体期血清 FSH 水平差异无统计学意义 (SMD = 0.22, 95% CI: -0.03 ~ 0.47, P = 0.09) (图 8)。

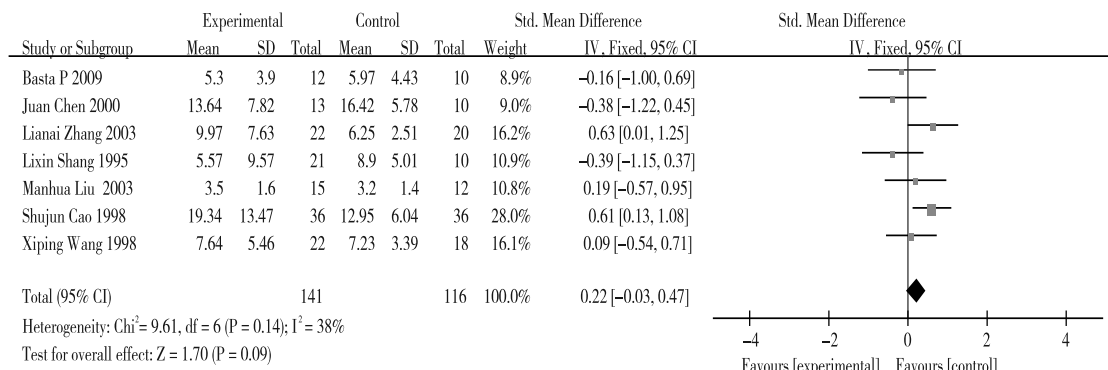


图 8 两组黄体期血清 FSH 水平比较的森林图
 Figure 8. Serum FSH during Luteal Phase in Two Groups

2.3.7 卵泡期血清 LH 水平 10 项研究^[12-13, 15, 18, 21-22, 25-27, 30], 其中子宫肌瘤组 980 例, 对照组 292 例, 各纳入研究同质 (I² = 48%), 采用固定效

应模型, 合并效应量结果显示子宫肌瘤患者卵泡期血清 LH 水平高于对照组 (SMD = 0.40, 95% CI: 0.24 ~ 0.55, P < 0.01) (图 9)。

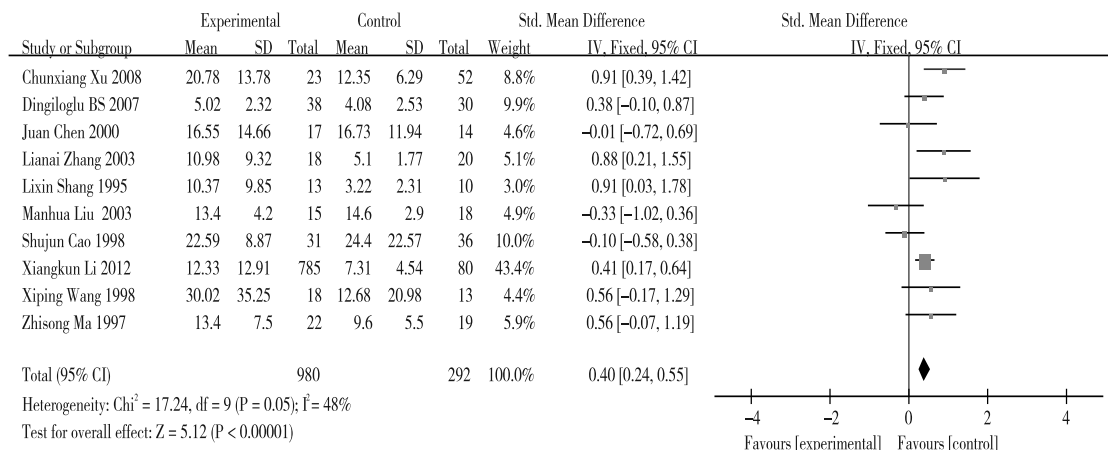


图 9 两组卵泡期血清 LH 水平比较的森林图
 Figure 9. Serum LH during Follicular Phase in Two Groups

2.3.8 黄体期血清 LH 水平 6 项研究^[12-13,22,25-26,30], 子宫肌瘤组 129 例, 对照组 106 例, 各纳入研究同质 ($I^2 = 0\%$), 采用固定效应模型, 合

并效应量结果显示两组黄体期血清 LH 水平差异无统计学意义 ($SMD = -0.11, 95\% CI: -0.37 \sim 0.15, P = 0.42$) (图 10)。

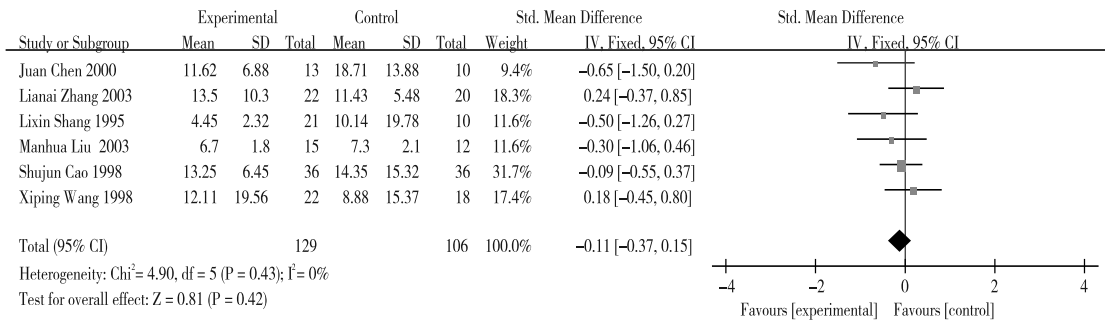


图 10 两组卵泡期血清 LH 水平比较的森林图
Figure 10. Serum LH during Luteal Phase in Two Groups

2.3 敏感性分析

对卵泡期血清雌激素水平的各纳入研究逐一剔除, 发现剔除前后的合并效应量变化不大且结论不变, 说明合并的研究结果稳定性较好 (图 11)。对卵泡期和黄体期其他血清激素水平采用相同的敏感性分析方法, 结果均表明敏感性较低, 研究结果稳健可信。

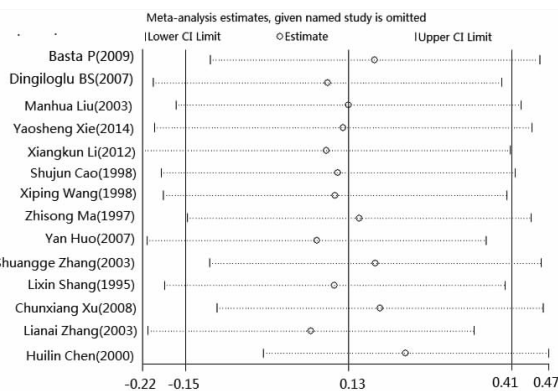


图 11 卵泡期血清雌激素水平的敏感性分析图
Figure 11. Sensitivity of Serum Estrogen during Follicular Phase

2.4 发表偏倚评估

通过 Egger's 检验对各研究纳入的文献进行发表偏倚分析, 结果显示卵泡期血清雌激素、FSH、LH 和黄体期血清雌激素、孕激素、LH 水平的 Egger's 检验 $P > 0.05$, 发表偏倚可能性较小; 卵泡期血清孕激素和黄体期血清 FSH 水平的 Egger's 检验 $P < 0.05$, 提示可能存在发表偏倚, 详见表 3。

3 讨论

子宫肌瘤是女性生殖器最常见的良性肿瘤^[31], 大量研究提示其发生发展可能与体内激素调节失衡相关。2015 年 Wong 等^[3] 研究发现, 较高血清水平

的雌激素合并睾酮可增加中年女性发生子宫肌瘤的风险, 但却减少纤维瘤复发。然而, 单独血清雌激素水平变化与子宫肌瘤的发生无统计学意义, 这可能与局部雌激素受体增加^[8] 和芳香化酶的过度表达相关。本研究结果显示, 子宫肌瘤患者与非子宫肌瘤人群相比, 血清雌、孕激素水平无明显差异。有研究表明雌激素可通过与其受体结合增加肌瘤组织孕激素受体的表达, 从而增强孕激素的敏感性, 孕激素通过调节一系列基因的表达促进肌瘤细胞的增殖及细胞外基质的形成, 减少凋亡, 已分化的肌瘤细胞可通过旁分泌的方式调节肌瘤干祖细胞的生长, 孕激素受体拮抗剂米非司酮与选择性孕酮受体调节剂醋酸乌利司他对子宫肌瘤的治疗有一定的疗效^[2,9,32-37]。

表 3 各研究因素发表偏倚的检验结果

Table 3. Publication Bias of Each Factor

Factor		Egger's test	
		t value	P value
Follicular phase	Estrogen	-1.18	0.261
	Progesterone	-2.27	0.046
	FSH	1.17	0.271
	LH	0.16	0.876
Luteal phase	Estrogen	0.16	0.878
	Progesterone	0.28	0.791
	FSH	-3.37	0.020
	LH	-1.54	0.220

女性体内激素水平的调节是一个复杂过程, 主要受下丘脑-垂体-卵巢轴的神经内分泌调控。FSH、LH 是由垂体分泌的促性腺激素, 促进卵泡发育、排卵及雌激素、孕激素的分泌, 其产生受下丘脑促性腺激素释放激素 (gonadotropin-releasing hormone, Gn-

RH)调节,同时受卵巢雌激素、孕激素、抑制素的反馈调控^[38],在卵泡早期(经期2~3天)血清呈低水平,排卵前迅速升高^[39]。本次 Meta 分析结果显示子宫肌瘤患者卵泡期血清 FSH、LH 水平高于非子宫肌瘤人群,与部分已有研究结果一致。Baird 等^[40]通过检测卵泡早期尿液 LH 水平发现,较高水平的 LH 与子宫肌瘤的发生相关,但与肌瘤的生长无明显相关性。相关研究表明 LH 除了可促进卵巢激素分泌外,还可通过与子宫肌层组织中的 LH 受体或绒毛膜促性腺激素(HCG)受体作用促进肌瘤的发生^[41],围绝经期肌瘤的迅速增长可能与体内 LH 水平波动有关^[42]。Plewka 等^[7]研究证实育龄期子宫肌瘤患者肌瘤组织 FSH、LH 受体水平高于子宫肌层。促性腺激素释放激素类似物(GnRH-a)可抑制 FSH、LH 分泌,降低血清雌激素水平,从而缓解临床症状并抑制肌瘤生长使其萎缩^[43-44]。因此,卵泡期血清 FSH、LH 水平可作为子宫肌瘤发病风险的预测因素,对于检测值较高的女性可采用有效的方法降低其水平,从而降低肌瘤的发生风险。但目前国内外对增加子宫肌瘤发生风险的血清 FSH、LH 水平阈值的判定仍无统一的明确标准,未来仍需进一步研究检测证实。

虽然本研究对纳入的文献进行了严格筛选,敏感性分析显示结果稳定性较好,且多项研究存在发表偏倚的可能性较小,但仍存在一些不足之处:(1)部分研究人群的年龄、标本检测方法等存在差异,部分研究存在异质性,采用随机效应模型;(2)符合标准的纳入文献中,近几年研究较少,部分研究结果可能存在发表偏倚,需纳入更多高质量文献;(3)各研究中有关子宫肌瘤的数目、大小、部位等数据缺乏,未做分析;(4)体内激素水平呈周期性变化,且 FSH、LH 在体内呈脉冲式分泌,采血时间不同可能影响 Meta 分析结果;(5)未对年龄等影响激素水平的因素进行亚组分析。

综上所述,卵泡期血清 FSH、LH 水平较高的女性有较高的子宫肌瘤发病风险,卵泡期血清雌激素、孕激素和黄体期血清雌激素、孕激素、FSH、LH 水平与子宫肌瘤的发生无显著联系,但仍需进一步研究支持,为疾病的发生风险评估及防治提供可靠依据。

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