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辅助生殖技术中绒毛膜下血肿的研究进展

许晓媛，李思然，崔　娜*

河北医科大学第二医院生殖医学科，河北　石家庄

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摘　要

绒毛膜下血肿(subchorionic hematoma, SCH)是指绒毛膜板与底蜕膜之间分离出血，而血液积聚在绒毛膜和底蜕膜之间形成的血肿。SCH在妊娠早期的超声检查中并不少见。既往的疾病、自身免疫性疾病和激素水平都可能与SCH有关，但其病因尚不清楚。有研究表明体外受精(*in-vitro* fertilization, IVF)是SCH发生的危险因素，且IVF助孕患者妊娠期发生SCH与不良妊娠结局关系密切。故本文针对IVF助孕患者从SCH的发病机制、诊断标准、危险因素、妊娠结局及治疗等方面进行综述，以期为临床诊治提供启示。

关键词

绒毛膜下血肿，体外受精，研究进展

Advances in the Study of Subchorionic Hematoma in Assisted Reproductive Technology

Xiaoyuan Xu, Siran Li, Na Cui*

Department of Reproductive Medicine, The Second Hospital of Hebei Medical University, Shijiazhuang Hebei

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Abstract

Subchorionic hematoma (SCH) is a kind of hematoma that forms when blood separates between the chorionic plate and the underlying metaplasm and accumulates between the chorion and the underlying metaplasm. It is common to see this on ultrasound in early pregnancy. Pre-existing medical conditions, autoimmune diseases and hormone levels may be associated with SCH, but its

*通讯作者。

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etiology is unknown. *In vitro* fertilization (IVF) has been shown to be a risk factor for the development of SCH, and the occurrence of SCH during pregnancy in IVF-assisted patients is strongly associated with poor pregnancy outcomes. Therefore, this paper reviews the pathogenesis, diagnostic criteria, risk factors, pregnancy outcome and treatment of SCH in patients with IVF assisted conception, in order to provide insight for clinical management.

Keywords

Subchorionic Hematoma (SCH), *In-Vitro* Fertilization (IVF), Research Progress

1. 引言

绒毛膜下血肿(subchorionic hematoma, SCH)是指绒毛膜板和底蜕膜之间分离引起的出血，文献中记录的 SCH 发病率差异较大，从 4%到 48%不等[1]。然而临床对 SCH 的认识存在较大争议，部分学者认为血肿随着妊娠的进展将被逐渐吸收，无需特殊治疗；也有学者认为 SCH 是不良妊娠结局的风险来源，应积极治疗。几项研究报道了 SCH 与不良妊娠和围产儿结局的关系，如自然流产、死产、胎盘早剥、早产、胎儿生长受限和胎膜早破[2]-[8]。我们发现，与自然妊娠相比，体外受精(*in vitro* fertilization, IVF)妊娠中 SCH 更常见[9] [10] [11]。本文针对 IVF-ET 后 SCH 的发病机制、病因及治疗的研究进展进行阐述，供临床医生参考。

2. SCH 的发病机制

SCH 形成的确切机制尚不确定，可能由于母胎界面的免疫调节机制紊乱，滋养细胞侵入蜕膜异常，导致胎盘血管重铸不良。另外免疫攻击引起的免疫性血管炎症可能造成凝血因子活化，增加微血栓的形成，血管栓塞以及后续的缺血再灌注损伤引起的出血都参与了 SCH 的发生，这也可能导致异常胎盘形成[3] [4] [6]。此外，在母胎界面的免疫调节机制中，Th1 和 Th2 细胞之间的平衡发挥关键的作用，尤其是在怀孕期间[12]。当胎儿与母体界面发生免疫冲突，致 Th1 细胞占优势，使得损伤性细胞与保护性细胞间的平衡被打破，血管凝血障碍，蜕膜血管发生破裂，形成 SCH [13]。而 Th1 和 Th2 细胞间的失衡会启动并强化参与自然流产、早产和先兆子痫的炎性细胞因子的级联产生[14]。

3. SCH 的临床表现及诊断标准

大多数患有绒毛膜下血肿的女性会出现一些阴道出血[15]，常为暗红色或血性白带样，少数患者量多，鲜红色，出血数小时甚至数周，伴或不伴有轻度下腹痛、腰痛、阵发性腹痛，且大多在妊娠早、中期发生。妇科查体可见宫口未开，无妊娠物排出。但有些女性根本不会出现任何出血。

由于 SCH 的临床表现没有特异性，并且可以发生在妊娠的任何时期，因此 SCH 的诊断多数依靠超声检查。SCH 通常为分隔子宫壁和绒毛膜的新月形低回声区域[16]，区别于急性出血的高回声或等回声。回声的高低与出血时间相关，若出血停止，血肿回声随病程进展逐渐减低。若处于血肿急性期(0~48 h)，血肿回声高于妊娠囊壁或叶状绒毛膜。若处于血肿亚急性期(3~7 d)，血肿回声近似于妊娠囊壁或叶状绒毛膜，血肿内回声表现复杂，如纤维条带样、团块状等。若出于血肿慢性期(>7 d)，血肿呈

低或无回声。最好每 1~2 周监测 B 超一次，若血肿增大，则提示病情加剧；血肿吸收缩小，提示病情缓解好转，一直监测至血肿消失。值得注意的是，SCH 还需要与肿瘤、双胎妊娠和早孕晚期绒毛膜与羊膜未融合相鉴别[17]。

描述 SCH 的方法在不同的报道中有很大不同。一些研究报告了 SCH 的大小，即被血肿包围的孕囊周长的百分比[18] [19] [20] [21]；一些人根据 SCH 大小主观分类为小、中或大[22]；还有人估计了 SCH 与孕囊的相对体积[3] [18] [19] [20] [21] [23]或通过公式计算 SCH 的体积[6] [18] [19] [24] [25]。临床常用的主要有以下两种方法：血肿/孕囊面积比例法：即血肿/孕囊面积 < 1/3 为轻度，1/3~1/2 为中度，>2/3 属于重度；血肿/孕囊体积比例法：<10%，11%~25%，26%~50%，>50%四个等级[26]。诊断时更常应用分度法：小于孕囊周边的 1/3 为轻度，达到孕囊周边的 1/3~1/2 为中度，大于孕囊周边的 1/2 为重度。

4. IVF 中 SCH 的病因

4.1. 控制性卵巢刺激(Controlled Ovarian Stimulation, COS)

SCH 在 IVF 助孕患者中发病率高[9]，这可能由于在 COS 中超生理水平的血清雌二醇可能会导致内膜的形态、生理和微环境的变化，从而损害新鲜周期移植患者的子宫内膜容受性，一方面可能会对着床和妊娠率产生不利影响[27]，另一方面高雌激素影响早期发育的胚胎的种植，可能导致植入和胎盘形成不充分[28] [29]，从而导致 SCH 的发生及后续胎盘发育不良。Esh-Broder 等人[30]回顾了 752 例 IVF 妊娠，发现 IVF 妊娠的胎盘植入率显著高于自然妊娠。而 IVF 妊娠中胎盘异常引起的产科并发症发生率较高的原因尚不完全清楚，推测也可能与 COS 中的高雌激素水平有关系。

4.2. 鲜胚移植或冻胚移植

一项对 1097 例 IVF 病例的回顾性队列研究表明，SCH 可能与鲜胚移植有关[31]。Ma 等人通过多元逻辑回归分析发现鲜胚移植是 SCH 发生的危险因素[32]。原因可能是接受鲜胚移植患者卵巢刺激及体内高雌二醇水平。高雌二醇浓度及卵巢刺激使得子宫内膜容受性降低[33]，孕早期血管生成障碍、胎盘形成不佳，边缘血管可能破裂形成血肿。还有研究认为鲜胚移植后，与妊娠相关血浆蛋白 A (PAPP-A)分泌减少[28]，而 PAPP-A 是由胎盘组织细胞及滋养细胞合成分泌的大分子糖蛋白，可诱导细胞外基质重塑，对于妊娠早期的血管生成和胎盘的形成至关重要。PAPP-A 的分泌降低也可能导致鲜胚周期 SCH 发生的原因之一。

另外，大多数研究结果显示，冷冻胚胎移植(frozen-thawed embryo transfer, FET)后产科并发症的发生率显著减少[34] [35]。然而，一项研究得出了相反的趋势，与鲜胚移植相比，FET 后 SCH 的发生率更高[9]。鉴于关于 FET 的研究都是激素替代周期(hormone replacement therapy, HRT)，因此妊娠结局可能与激素替代周期期间子宫内膜环境的改变有关。另外有研究证明，与自然周期相比，HRT 中 SCH 的发生率高、出血增加[28] [36]。与 COS 相比，HRT 患者的雌激素水平较低。因此我们推测，在 FET 中，除了由外源性雌激素引起的子宫内膜环境改变以外的其他因素也会影响着床和胎盘的形成。Sazonova 等人[35]比较了 FET (2348 周期)和鲜胚移植(8944 周期)后产科并发症的发生率，发现 FET 组妊娠高血压综合征(pregnancy-induced hypertension, PIH)的发生率较高。此外，Ishihara 等人[37]比较了大样本量的 FET (151,998 个周期)和鲜胚移植(125,044 个周期)，也发现 FET 与 PIH 的发生有关。尽管目前对 PIH 的病因存在争议，但主要的假说是，一些胎盘疾病或免疫问题，会引起与血管生成相关因子的变化，如孕妇血管内皮生长因子(vascular endothelial growth factor, VEGF)、胎盘生长因子和血清可溶性 VEGF 受体-1，这些血管生成因子可能会导致母体进一步的胎盘功能不足和系统性疾病[38]。尽管这一假说并不完全适用，但 FET 组 SCH 的高发生率很可能是由于 FET 过程中植入环境的变化造成底蜕膜没有牢固的侵入子宫壁，

导致底蜕膜和子宫壁之间的结构不牢固，导致血肿的发生。因此，需要更大样本量的研究来证实 FET 后 SCH 的高发生率，并阐明潜在的原因。

4.3. 囊胚移植

有研究表明囊胚移植也是 IVF 中发生 SCH 的危险因素[9]，Fernando 等人[39]发现囊胚移植后的女性发生先兆子痫和前置胎盘的风险略高。并且，有证据说明与卵裂期胚胎移植相比，囊胚移植后早产和大于胎龄儿(large for gestational age, LGA)的风险显著增加[40] [41]，推测延长胚胎培养可能导致异常的植入和胎盘形成，影响滋养外胚层细胞的基因和表观。在囊胚移植中，移植滋养外胚层较低级别的囊胚后的妊娠易出现 SCH，已知滋养细胞 TE 分级和 IVF 结局相关[42] [43] [44]，因此滋养外胚层 A 级的囊胚，可能可以一定程度减少 SCH 及其相关并发症的发生。但是此类研究的样本量较小，需要更大样本量的研究来确定。

4.4. 多囊卵巢综合症(Polycystic Ovary Syndrome, PCOS)

有研究发现 PCOS 是 IVF 助孕人群发生 SCH 的独立危险因素[32]。PCOS 患者异常的代谢和激素水平可能通过影响子宫内膜容受性诱发 SCH [45]。另一些研究表明，整合素及白细胞介素、MECA-79 的免疫分子在 PCOS 患者中表达降低也是引起 SCH 的因素之一[45] [46]。仍然需要大样本的试验进一步探索。

4.5. 输卵管积水

输卵管积水的患者一般会接受输卵管结扎或切除的治疗，避免输卵管积水对子宫内膜的侵蚀作用。虽然输卵管积水无法返回宫腔，但是一些潜在致病因素，如细胞因子、前列腺素、白细胞介素等通过淋巴和血液循环作用到邻近器官，危害子宫内膜的功能，降低子宫内膜容受性[47] [48]。仅一项研究报道输卵管积水是 SCH 的危险因素[32]，但机制尚不清楚。

5. SCH 的临床结局

5.1. 孕妇年龄与妊娠结局

不同年龄女性发生 SCH 的结局有明显差异。高龄孕妇胎盘附着于子宫壁上需要更多的营养物质和血供，而机体自身供求失衡，胎膜未牢牢附着于子宫壁，导致 SCH 的发生。有研究观察到，35 岁及以上妇女的自然流产率约为年轻妇女的两倍(13.8% vs. 7.3%) [21] [26]，提示 SCH 的高龄妇女产生不良结局的风险大于低龄妇女。高龄孕妇不良妊娠结局风险的增加主要归因于并存的其他疾病，如代谢综合征、既往癌症病史、心血管、肾脏和自身免疫性疾病。

5.2. 诊断时的胎龄(Gestational Age, GA)与妊娠结局

有研究发现，孕 9 周前被诊断为 SCH 的妇女流产率约为 20%，而在此孕龄之后被诊断 SCH 的妇女，流产的可能性要小得多(不到 2%) [6] [49]。也有研究发现孕 8 周及以前妊娠丢失的风险为 17.3%，8 周后风险降为 3.6% [26]。

5.3. 血肿大小及部位与妊娠结局

血肿量及血肿部位可能影响妊娠结局。关于多普勒超声的研究显示，血肿扩大与螺旋动脉血流速度减慢有显著关系，对维持妊娠有潜在的威胁[50]。但是，关于血肿量和妊娠结局之间的关系尚存在争议。有研究显示“大”血肿与不良妊娠结局之间有显著的相关性[51] [52]，也有研究并未明确指出[6]。Bennett 等人[21]的研究将血肿引起的孕囊周长大于孕囊周长的 2/3 定义为大体积，此“大”血肿导致自然流产的

风险增加 2.4 倍。因此，不同研究结果的差异可能是由于对血肿“大小”的随意定义，未给出统一的评判标准。通过宫颈的出血量并不完全等于绒毛膜下出血量。因此，血肿大小不能代表其严重程度，最终只能通过子宫中出血、再吸收和通过宫颈的失血量来评估病情。我们可以在此基础上推测血肿的存在及位置，作为胎盘受损的标志，对妊娠结局的预测至关重要[26]。一些人评估了 SCH 在子宫中的位置[3] [23] [24] [50] [53]并发现，SCH 出现在宫底部比较严重，不良妊娠结局发生率由高到低依次为：宫底部 > 子宫前、后壁 > 宫颈口。原因可能是子宫颈处血肿在妊娠过程中被溶解、吸收，或慢慢从宫颈排出，而宫底部血肿不能从宫颈流出，血肿可能越来越大，另外，长期的出血也增加宫内感染的机会，导致病情越来越重[54]。

5.4. SCH 与妊娠并发症

有研究发现 IVF 妊娠妇女 SCH 的发生与自然流产率的增加有关[32]。但是，Zhou 等人发现与自然妊娠相比，IVF/ICSI 后 SCH 的妇女妊娠失败的几率并未增加[31]。发生 SCH 与无 SCH 的 IVF 妊娠女性相比，流产率并未增加[55]。另外，有研究认为 SCH 与早产、自然流产、妊高症的发生无关[56] [57]。因此，血肿对妊娠结局的影响尚存争议。

5.5. SCH 与胎儿及胎儿附属物异常

有报道发现与接受 IVF 以外的不孕症治疗的非 IVF 组相比，IVF 组的产前出血和前置胎盘的发生率更高[28]。IVF 妊娠与自然妊娠相比，SCH 与单胎妊娠的低出生体重有关[31]。另外，也有学者认为，SCH 未增加胎膜早破、胎盘早剥，死产，胎儿生长受限的风险[56]。SCH 对新生儿结局的影响有待进一步研究。

6. 绒毛膜下大量血肿(Massive Subchorionic Hematoma, MSH)

MSH 是一种巨大的母体血液凝块，厚度至少 1 厘米，将绒毛膜板和孕囊分开[58]。这种疾病的发病率很低，约 0.03%~0.08% [59]。MSH 的发生与不良妊娠结局有关，如胎儿生长受限(FGR)和胎儿宫内死亡(IUFD) [59] [60] [61]。也有研究报道 MSH 与胎儿生长受限、先兆子痫、胎儿窘迫、胎盘早剥、早产等不良妊娠结局相关[59] [62] [63] [64]。此类疾病几乎都是以病例报告的形式报道，这也是其病理生理仍不清楚的原因。有病例报道出 MSH 伴随着胎盘肥大，虽然胎盘肥大通常是由绒毛增大引起的，但是具体原因有：积水、梅毒、弓形虫病、巨细胞病毒或微小病毒、胎盘间质发育不良[65] [66]。当出现不明原因胎盘肥大时，应把 MSH 视为鉴别诊断。磁共振成像对 MSH 的诊断和随访是有用的，结合多普勒超声检查观察胎盘内液－液平面的发展情况。有报道说液－液平面发生在血肿的早期阶段[61]；也有病例的液－液水平是连续出血后的沉淀效应引起的。因此，影像学表现暂未发现特异性指标[67]。

7. SCH 的治疗

SCH 在临床中并不少见，但是暂无相关指南指导治疗。首先应结合病人个体情况进行全面评估，在病情允许条件下，保持积极向上的良好心态，良好的生活方式，卧床休息[68]，避免过度焦虑，观察是否伴随宫缩。如有宫缩，可应用间苯三酚、硫酸镁、阿托西班等抑制宫缩。

妊娠早期的 SCH 主要依靠机体自身对血肿的吸收来修复，对于中至大型的 SCH 患者，以促进血肿吸收、对症治疗为主。低分子肝素作为高效抗凝剂，具有抑制凝血酶及凝血活性因子的作用，通过增加抗凝血酶的活性，保护血管壁，以改善胎盘血液循环。阿司匹林属于非甾体类抗炎药，其应用可明显改善血液的高凝状态，有效抑制血小板凝集，预防血栓的形成，改善局部血液循环，降低子宫动脉血流阻力，促进前列环素与血栓素平衡，增加胎盘血流，从而促进胚胎生长。因这两种药物具有强效抗栓作用，

联合使用可使血肿情况得到改善。若血肿持续增大的情况下，可暂停低分子肝素，加用宫缩抑制剂和止血药，例如氨甲环酸、安络血等，必要时使用抗生素预防感染。另外，地屈孕酮被发现在维持 Th2 细胞因子平衡方面具有免疫调节作用，也有一定治疗作用[69]。现有研究证实低分子肝素联合免疫球蛋白有可观的治疗作用[70] [71]。此外，最新研究发现硫辛酸[72] [73]作为一种免疫调节剂，可以纠正 SCH 患者体内的免疫失衡，促进血肿吸收。

8. 小结

综上所述，辅助生殖技术治疗后出现 SCH 的机制尚未明确，其对妊娠结局的影响也未明确。对于此类 SCH 患者，临床医生应密切关注，安抚患者，引导患者积极面对以减少不良妊娠结局的发生。最新的研究[32]创建了预测 SCH 发生及结局的列线图，为临床医生的处理提供参考。对于其他变量，如多囊卵巢综合征、薄型子宫内膜、输卵管积水等是否是 SCH 的危险因素，仍待进一步研究。应积极探讨 IVF 人群 SCH 的发病机制，紧密结合 SCH 的进展，改善母婴预后。

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参考文献

[1] Khan, R.I., Taimoor, A., Nazir, A., Zaman, U., Azmat, S. and Nawaz, F. (2021) Association of Subchorionic Hematoma with Preterm Labour in Patients with Threatened Abortion. *Journal of Ayub Medical College, Abbottabad*: *JAMC*, **33**, 451-455.

[2] Tuuli, M.G., Norman, S.M., Odibo, A.O., Macones, G.A. and Cahill, A.G. (2011) Perinatal Outcomes in Women with Subchorionic Hematoma: A Systematic Review and Meta-Analysis. *Obstetrics and Gynecology*, **117**, 1205-1212. https://doi.org/10.1097/AOG.0b013e31821568de

[3] Nagy, S., Bush, M., Stone, J., Lapinski, R.H. and Gardó, S. (2003) Clinical Significance of Subchorionic and Retroplacental Hematomas Detected in the First Trimester of Pregnancy. *Obstetrics and gynecology*, **102**, 94-100. https://doi.org/10.1097/00006250-200307000-00019

[4] Sharma, G., Kalish, R.B. and Chasen, S.T. (2003) Prognostic Factors Associated with Antenatal Subchorionic Echolucencies. *American Journal of Obstetrics and Gynecology*, **189**, 994-996. https://doi.org/10.1067/S0002-9378(03)00823-8

[5] Norman, S.M., Odibo, A.O., Macones, G.A., Dicke, J.M., Crane, J.P. and Cahill, A.G. (2010) Ultrasound-Detected Subchorionic Hemorrhage and the Obstetric Implications. *Obstetrics and Gynecology*, **116**, 311-315. https://doi.org/10.1097/AOG.0b013e3181e90170

[6] Maso, G., D'Ottavio, G., De Seta, F., Sartore, A., Piccoli, M. and Mandruzzato, G. (2005) First-Trimester Intrauterine Hematoma and Outcome of Pregnancy. *Obstetrics and Gynecology*, **105**, 339-344. https://doi.org/10.1097/01.AOG.0000152000.71369.bd

[7] Şükür, Y.E., Göç, G., Köse, O., *et al.* (2014) The Effects of Subchorionic Hematoma on Pregnancy Outcome in Patients with Threatened Abortion. *Journal of the Turkish German Gynecological Association*, **15**, 239-242. https://doi.org/10.5152/jtgga.2014.14170

[8] Naz, S., Irfan, S., Naru, T. and Malik, A. (2022) Subchorionic Hematoma and Pregnancy Outcomes in Patients with Threatened Miscarriage. *Pakistan Journal of Medical Sciences*, **38**, 511-516. https://doi.org/10.12669/pjms.38.3.4283

[9] Asato, K., Mekaru, K., Heshiki, C., *et al.* (2014) Subchorionic Hematoma Occurs More Frequently in *in Vitro* Fertilization Pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, **181**, 41-44. https://doi.org/10.1016/j.ejogrb.2014.07.014

[10] Frates, M.C., Benson, C.B. and Doubilet, P.M. (1993) Pregnancy Outcome after a First Trimester Sonogram Demonstrating Fetal Cardiac Activity. *Journal of Ultrasound in Medicine*: *Official Journal of the American Institute of Ultra-*

sound in Medicine, **12**, 383-386. https://doi.org/10.7863/jum.1993.12.7.383

[11] Xiang, L., Wei, Z., Wu, J., Zhou, P., Xiang, H. and Cao, Y. (2014) Clinical Significance of First-Trimester Intrauterine Haematomas Detected in Pregnancies Achieved by IVF-Embryo Transfer. *Reproductive Biomedicine Online*, **29**, 445-451. https://doi.org/10.1016/j.rbmo.2014.06.015

[12] Lee, S.K., Kim, J.Y., Lee, M., Gilman-Sachs, A. and Kwak-Kim, J. (2012) Th17 and Regulatory T Cells in Women with Recurrent Pregnancy Loss. *American Journal of Reproductive Immunology*: *AJRI*: *Official Journal of the American Society for the Immunology of Reproduction and the International Coordination Committee for Immunology of Reproduction*, **67**, 311-318. https://doi.org/10.1111/j.1600-0897.2012.01116.x

[13] 陈秋连, 张雨婷, 艾冬冬. 孕激素诱导封闭因子在绒毛膜下血肿患者体内的表达及与 Th1/Th2 细胞因子的相关性[J]. 中国当代医药, 2023, 30(12): 82-85,89.

[14] Challis, J.R., Lockwood, C.J., Myatt, L., Norman, J.E., Strauss, J.F. 3rd and Petraglia, F. (2009) Inflammation and Pregnancy. *Reproductive Sciences* (*Thousand Oaks, Calif.*), **16**, 206-215. https://doi.org/10.1177/1933719108329095

[15] Aki, M., Katsumata, M., Yamanoi, K., *et al.* (2022) The Significance of Clinical Symptoms of Subchorionic Hematomas, "Bleeding First", to Stratify the High-Risk Subgroup of Very Early Preterm Delivery. *Taiwanese Journal of Obstetrics & Gynecology*, **61**, 243-248. https://doi.org/10.1016/j.tjog.2022.02.011

[16] Peixoto, A.B., Caldas, T., Petrini, C.G., *et al.* (2018) The Impact of First-Trimester Intrauterine Hematoma on Adverse Perinatal Outcomes. *Ultrasonography*, **37**, 330-336. https://doi.org/10.14366/usg.18006

[17] Liu, Y., Tong, A. and Qi, X. (2020) A Large Subchorionic Hematoma in Pregnancy: A Case Report. *Medicine*, **99**, e20280. https://doi.org/10.1097/MD.0000000000020280

[18] Abu-Yousef, M.M., Bleicher, J.J., Williamson, R.A. and Weiner, C.P. (1987) Subchorionic Hemorrhage: Sonographic Diagnosis and Clinical Significance. *AJR. American Journal of Roentgenology*, **149**, 737-740. https://doi.org/10.2214/ajr.149.4.737

[19] Sauerbrei, E.E. and Pham, D.H. (1986) Placental Abruption and Subchorionic Hemorrhage in the First Half of Pregnancy: US Appearance and Clinical Outcome. *Radiology*, **160**, 109-112. https://doi.org/10.1148/radiology.160.1.3520643

[20] Dickey, R.P., Olar, T.T., Curole, D.N., Taylor, S.N. and Matulich, E.M. (1992) Relationship of First-Trimester Subchorionic Bleeding Detected by Color Doppler Ultrasound to Subchorionic Fluid, Clinical Bleeding, and Pregnancy Outcome. *Obstetrics and Gynecology*, **80**, 415-420.

[21] Bennett, G.L., Bromley, B., Lieberman, E. and Benacerraf, B.R. (1996) Subchorionic Hemorrhage in First-Trimester Pregnancies: Prediction of Pregnancy Outcome with Sonography. *Radiology*, **200**, 803-806. https://doi.org/10.1148/radiology.200.3.8756935

[22] Benson, C.B., Doubilet, P.M., Cooney, M.J., Frates, M.C., David, V. and Hornstein, M.D. (1997) Early Singleton Pregnancy Outcome: Effects of Maternal Age and Mode of Conception. *Radiology*, **203**, 399-403. https://doi.org/10.1148/radiology.203.2.9114094

[23] Leite, J., Ross, P., Rossi, A.C. and Jeanty, P. (2006) Prognosis of Very Large First-Trimester Hematomas. *Journal of Ultrasound in Medicine*: *Official Journal of the American Institute of Ultrasound in Medicine*, **25**, 1441-1445. https://doi.org/10.7863/jum.2006.25.11.1441

[24] Pedersen, J.F. and Mantoni, M. (1990) Prevalence and Significance of Subchorionic Hemorrhage in Threatened Abortion: A Sonographic Study. *AJR. American Journal of Roentgenology*, **154**, 535-537. https://doi.org/10.2214/ajr.154.3.2106217

[25] Rizzo, G., Capponi, A., Soregaroli, M., Arduini, D. and Romanini, C. (1995) Early Fetal Circulation in Pregnancies Complicated by Retroplacental Hematoma. *Journal of Clinical Ultrasound*: *JCU*, **23**, 525-529. https://doi.org/10.1002/jcu.1870230904

[26] Heller, H.T., Asch, E.A., Durfee, S.M., *et al.* (2018) Subchorionic Hematoma: Correlation of Grading Techniques with First-Trimester Pregnancy Outcome. *Journal of Ultrasound in Medicine*: *Official Journal of the American Institute of Ultrasound in Medicine*, **37**, 1725-1732. https://doi.org/10.1002/jum.14524

[27] Arslan, M., Bocca, S., Arslan, E.O., Duran, H.E., Stadtmauer, L. and Oehninger, S. (2007) Cumulative Exposure to High Estradiol Levels during the Follicular Phase of IVF Cycles Negatively Affects Implantation. *Journal of Assisted Reproduction and Genetics*, **24**, 111-117. https://doi.org/10.1007/s10815-006-9101-x

[28] Healy, D.L., Breheny, S., Halliday, J., *et al.* (2010) Prevalence and Risk Factors for Obstetric Haemorrhage in 6730 Singleton Births after Assisted Reproductive Technology in Victoria Australia. *Human Reproduction* (*Oxford, England*), **25**, 265-274. https://doi.org/10.1093/humrep/dep376

[29] Horcajadas, J.A., Riesewijk, A., Polman, J., *et al.* (2005) Effect of Controlled Ovarian Hyperstimulation in IVF on Endometrial Gene Expression Profiles. *Molecular Human Reproduction*, **11**, 195-205. https://doi.org/10.1093/molehr/gah150

[30] Esh-Broder, E., Ariel, I., Abas-Bashir, N., Bdolah, Y. and Celnikier, D.H. (2011) Placenta Accreta Is Associated with IVF Pregnancies: A Retrospective Chart Review. *BJOG*: *An International Journal of Obstetrics and Gynaecology*, **118**, 1084-1089. https://doi.org/10.1111/j.1471-0528.2011.02976.x

[31] Zhou, J., Wu, M., Wang, B., *et al.*(2017) The Effect of First Trimester Subchorionic Hematoma on Pregnancy Outcomes in Patients Underwent IVF/ICSI Treatment. *The Journal of Maternal-Fetal & Neonatal Medicine*: *The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, **30**, 406-410. https://doi.org/10.1080/14767058.2016.1174682

[32] Yue, M., Ma, L., Cao, Y. and Zhai, J. (2021) Application of a Nomogram for Predicting the Risk of Subchorionic Hematoma in Early Pregnancy with *in Vitro* Fertilization-Embryo Transfer/Frozen Embryo Transfer. *Frontiers in Endocrinology*, **12**, Article ID: 631097. https://doi.org/10.3389/fendo.2021.631097

[33] Shapiro, B.S., Daneshmand, S.T., Garner, F.C., Aguirre, M., Hudson, C. and Thomas, S. (2011) Evidence of Impaired Endometrial Receptivity after Ovarian Stimulation for *in Vitro* Fertilization: A Prospective Randomized Trial Comparing Fresh and Frozen-Thawed Embryo Transfer in Normal Responders. *Fertility and Sterility*, **96**, 344-348. https://doi.org/10.1016/j.fertnstert.2011.05.050

[34] Maheshwari, A., Pandey, S., Shetty, A., Hamilton, M. and Bhattacharya, S. (2012) Obstetric and Perinatal Outcomes in Singleton Pregnancies Resulting from the Transfer of Frozen Thawed versus Fresh Embryos Generated through *in Vitro* Fertilization Treatment: A Systematic Review and Meta-Analysis. *Fertility and Sterility*, **98**, 368-377.e1-9. https://doi.org/10.1016/j.fertnstert.2012.05.019

[35] Sazonova, A., Källen, K., Thurin-Kjellberg, A., Wennerholm, U.B. and Bergh, C. (2012) Obstetric Outcome in Singletons after *in Vitro* Fertilization with Cryopreserved/Thawed Embryos. *Human Reproduction* (*Oxford, England*), **27**, 1343-1350. https://doi.org/10.1093/humrep/des036

[36] Reich, J., Blakemore, J.K. and Grifo, J.A. (2020) Comparison of Subchorionic Hematoma in Medicated or Natural Single Euploid Frozen Embryo Transfer Cycles. *Fertility and Sterility*, **114**, 595-600. https://doi.org/10.1016/j.fertnstert.2020.04.040

[37] Ishihara, O., Araki, R., Kuwahara, A., Itakura, A., Saito, H. and Adamson, G.D. (2014) Impact of Frozen-Thawed Single-Blastocyst Transfer on Maternal and Neonatal Outcome: An Analysis of 277,042 Single-Embryo Transfer Cycles from 2008 to 2010 in Japan. *Fertility and Sterility*, **101**, 128-133. https://doi.org/10.1016/j.fertnstert.2013.09.025

[38] Kintiraki, E., Papakatsika, S., Kotronis, G., Goulis, D.G. and Kotsis, V. (2015) Pregnancy-Induced Hypertension. *Hormones* (*Athens, Greece*), **14**, 211-223. https://doi.org/10.14310/horm.2002.1582

[39] Fernando, D., Halliday, J.L., Breheny, S. and Healy, D.L. (2012) Outcomes of Singleton Births after Blastocyst versus Nonblastocyst Transfer in Assisted Reproductive Technology. *Fertility and Sterility*, **97**, 579-584. https://doi.org/10.1016/j.fertnstert.2011.12.032

[40] Dar, S., Librach, C.L., Gunby, J., Bissonnette, F. and Cowan, L. (2013) Increased Risk of Preterm Birth in Singleton Pregnancies after Blastocyst versus Day 3 Embryo Transfer: Canadian ART Register (CARTR) Analysis. *Human Reproduction* (*Oxford, England*), **28**, 924-928. https://doi.org/10.1093/humrep/des448

[41] Marconi, N., Allen, C.P., Bhattacharya, S. and Maheshwari, A. (2022) Obstetric and Perinatal Outcomes of Singleton Pregnancies after Blastocyst-Stage Embryo Transfer Compared with Those after Cleavage-Stage Embryo Transfer: A Systematic Review and Cumulative Meta-Analysis. *Human Reproduction Update*, **28**, 255-281. https://doi.org/10.1093/humupd/dmab042

[42] Luke, B., Brown, M.B., Stern, J.E., Jindal, S.K., Racowsky, C. and Ball, G.D. (2014) Using the Society for Assisted Reproductive Technology Clinic Outcome System Morphological Measures to Predict Live Birth after Assisted Reproductive Technology. *Fertility and Sterility*, **102**, 1338-1344. https://doi.org/10.1016/j.fertnstert.2014.07.1242

[43] Ebner, T., Tritscher, K., Mayer, R.B., *et al.* (2016) Quantitative and Qualitative Trophectoderm Grading Allows for Prediction of Live Birth and Gender. *Journal of Assisted Reproduction and Genetics*, **33**, 49-57. https://doi.org/10.1007/s10815-015-0609-9

[44] Hill, M.J., Richter, K.S., Heitmann, R.J., *et al.*(2013) Trophectoderm Grade Predicts Outcomes of Single-Blastocyst Transfers. *Fertility and Sterility*, **99**, 1283-1289.e1. https://doi.org/10.1016/j.fertnstert.2012.12.003

[45] Lopes, I.M., Maganhin, C.C., Oliveira-Filho, R.M., *et al.* (2014) Histomorphometric Analysis and Markers of Endometrial Receptivity Embryonic Implantation in Women with Polycystic Ovary Syndrome during the Treatment with Progesterone. *Reproductive Sciences* (*Thousand Oaks, Calif.*), **21**, 930-938. https://doi.org/10.1177/1933719113519169

[46] Piltonen, T.T., Chen, J.C., Khatun, M., *et al.* (2015) Endometrial Stromal Fibroblasts from Women with Polycystic Ovary Syndrome Have Impaired Progesterone-Mediated Decidualization, Aberrant Cytokine Profiles and Promote Enhanced Immune Cell Migration *in Vitro*. *Human Reproduction* (*Oxford, England*), **30**, 1203-1215. https://doi.org/10.1093/humrep/dev055

[47] Meyer, W.R., Castelbaum, A.J., Somkuti, S., *et al.* (1997) Hydrosalpinges Adversely Affect Markers of Endometrial

Receptivity. *Human Reproduction* (*Oxford, England*), **12**, 1393-1398. https://doi.org/10.1093/humrep/12.7.1393

[48] Li, L., Xu, B.F., Chen, Q.J. and Sun, X.X. (2010) Effects of Hydrosalpinx on Pinopodes, Leukaemia Inhibitory Factor, Integrin beta3 and MUC1 Expression in the Peri-Implantation Endometrium. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, **151**, 171-175. https://doi.org/10.1016/j.ejogrb.2010.04.024

[49] Naqvi, M., Naert, M.N., Khadraoui, H., *et al.*(2021) Subchorionic Hematomas and Adverse Pregnancy Outcomes among Twin Pregnancies. *American Journal of Perinatology*, **38**, 779-783. https://doi.org/10.1055/s-0039-3401852

[50] Kurjak, A., Schulman, H., Zudenigo, D., Kupesic, S., Kos, M. and Goldenberg, M. (1996) Subchorionic Hematomas in Early Pregnancy: Clinical Outcome and Blood Flow Patterns. *The Journal of Maternal-Fetal Medicine*, **5**, 41-44. https://doi.org/10.1002/(SICI)1520-6661(199601/02)5:1<41::AID-MFM10>3.0.CO;2-Q

[51] 吴丽静, 连成瑛. 不同孕周及不同程度的绒毛膜下血肿对妊娠结局的影响[J]. 福建医药杂志, 2021, 43(4): 53-55.

[52] 罗伟榕. 超声对先兆流产合并绒毛膜下血肿妊娠结局的预测价值体会[J]. 医学食疗与健康, 2020, 18(21): 172+174.

[53] Mantoni, M. and Pedersen, J.F. (1981) Intrauterine Haematoma. An Ultrasonic Study of Threatened Abortion. *British Journal of Obstetrics and Gynaecology*, **88**, 47-51. https://doi.org/10.1111/j.1471-0528.1981.tb00936.x

[54] Inman, E.R., Miranian, D.C., Stevenson, M.J., Kobernik, E.K., Moravek, M.B. and Schon, S.B. (2022) Outcomes of Subchorionic Hematoma-Affected Pregnancies in the Infertile Population. *International Journal of Gynaecology and Obstetrics*: *The Official Organ of the*, **159**, 743-750. https://doi.org/10.1002/ijgo.14162

[55] West, B.T., Kavoussi, P.K., Odenwald, K.C., *et al.* (2020) Factors Associated with Subchorionic Hematoma Formation in Pregnancies Achieved via Assisted Reproductive Technologies. *Journal of Assisted Reproduction and Genetics*, **37**, 305-309. https://doi.org/10.1007/s10815-019-01684-7

[56] Naert, M.N., Muniz Rodriguez, A., Khadraoui, H., Naqvi, M. and Fox, N.S. (2019) Association between First-Trimester Subchorionic Hematomas and Adverse Pregnancy Outcomes after 20 Weeks of Gestation in Singleton Pregnancies. *Obstetrics and Gynecology*, **134**, 863-868. https://doi.org/10.1097/AOG.0000000000003487

[57] Naert, M.N., Khadraoui, H., Muniz Rodriguez, A., Naqvi, M. and Fox, N.S. (2019) Association between First-Trimester Subchorionic Hematomas and Pregnancy Loss in Singleton Pregnancies. *Obstetrics and Gynecology*, **134**, 276-281. https://doi.org/10.1097/AOG.0000000000003360

[58] Shanklin, D.R. and Scott, J.S. (1975) Massive Subchorial Thrombohaematoma (Breus' Mole). *British Journal of Obstetrics and Gynaecology*, **82**, 476-487. https://doi.org/10.1111/j.1471-0528.1975.tb00673.x

[59] Alanjari, A., Wright, E., Keating, S., Ryan, G. and Kingdom, J. (2013) Prenatal Diagnosis, Clinical Outcomes, and Associated Pathology in Pregnancies Complicated by Massive Subchorionic Thrombohematoma (Breus' Mole). *Prenatal Diagnosis*, **33**, 973-978. https://doi.org/10.1002/pd.4176

[60] Fung, T.Y., To, K.F., Sahota, D.S., Chan, L.W., Leung, T.Y. and Lau, T.K. (2010) Massive Subchorionic Thrombohematoma: A Series of 10 Cases. *Acta Obstetricia et Gynecologica Scandinavica*, **89**, 1357-1361. https://doi.org/10.3109/00016349.2010.512656

[61] Nishijima, K., Shukunami, K., Tsuyoshi, H., *et al.* (2005) Massive Subchorionic Hematoma: Peculiar Prenatal Images and Review of the Literature. *Fetal Diagnosis and Therapy*, **20**, 23-26. https://doi.org/10.1159/000081364

[62] Nishida, N., Suzuki, S., Hamamura, Y., *et al.* (2001) Massive Subchorionic Hematoma (Breus' Mole) Complicated by Intrauterine Growth Retardation. *Journal of Nippon Medical School*, **68**, 54-57. https://doi.org/10.1272/jnms.68.54

[63] Nagy, S., Bush, M., Stone, J., Lapinski, R. and Gardó, S. (2005) Clinical Significance of Subchorionic and Retroplacental Hematomas Detected in the First Trimester of Pregnancy. *Orvosi Hetilap*, **146**, 2157-2161.

[64] El-Agwany, A.S. (2017) Large Subchorionic Hematoma: Breus' Mole. *Journal of Medical Ultrasound*, **25**, 248-250. https://doi.org/10.1016/j.jmu.2017.09.006

[65] Rac, M.W., Revell, P.A. and Eppes, C.S. (2017) Syphilis during Pregnancy: A Preventable Threat to Maternal-Fetal Health. *American Journal of Obstetrics and Gynecology*, **216**, 352-363. https://doi.org/10.1016/j.ajog.2016.11.1052

[66] Parveen, Z., Tongson-Ignacio, J.E., Fraser, C.R., Killeen, J.L. and Thompson, K.S. (2007) Placental Mesenchymal Dysplasia. *Archives of Pathology & Laboratory Medicine*, **131**, 131-137. https://doi.org/10.5858/2007-131-131-PMD

[67] Wang, L., Zhou, Q., Li, L. and Zeng, S. (2018) Unique Fluid-Fluid Level Ultrasonic Appearance in Subacute Placenta Abruption with Massive Subchorionic Hematoma. *International Journal of Gynaecology and Obstetrics*: *The Official Organ of the International Federation of Gynaecology and Obstetrics*, **141**, 391-392. https://doi.org/10.1002/ijgo.12474

[68] Ben-Haroush, A., Yogev, Y., Mashiach, R. and Meizner, I. (2003) Pregnancy Outcome of Threatened Abortion with Subchorionic Hematoma: Possible Benefit of Bed-Rest. *The Israel Medical Association Journal*: *IMAJ*, **5**, 422-424.

[69] Pelinescu-Onciul, D. (2007) Subchorionic Hemorrhage Treatment with Dydrogesterone. *Gynecological Endocrinology*: *The Official Journal of the International Society of Gynecological Endocrinology*, **23**, 77-81.

https://doi.org/10.1080/09513590701584741

[70] 李晓彬, 郭义红. 超声检测低分子肝素联合免疫球蛋白治疗绒毛膜下血肿的疗效和妊娠结局的临床价值[J]. 临床和实验医学杂志, 2017, 16(8): 803-806.

[71] 陈旭菲, 莫丽芳, 林彬, 梁逸仙, 林春明. 低分子肝素联合免疫球蛋白治疗复发性流产合并绒毛膜下血肿的疗效分析[J]. 中国现代药物应用, 2019, 13(16): 114-115.

[72] Costantino, M., Guaraldi, C. and Costantino, D. (2016) Resolution of Subchorionic Hematoma and Symptoms of Threatened Miscarriage Using Vaginal Alpha Lipoic Acid or Progesterone: Clinical Evidences. *European Review for Medical and Pharmacological Sciences*, **20**, 1656-1663.

[73] Di Tucci, C., Di Feliciantonio, M., Vena, F., *et al.* (2018) Alpha Lipoic Acid in Obstetrics and Gynecology. *Gynecological Endocrinology*: *The Official Journal of the International Society of Gynecological Endocrinology*, **34**, 729-733. https://doi.org/10.1080/09513590.2018.1462320