LAMPIRAN

Lampiran 1. Asuhan Kebidanan

ASUHAN KEBIDANAN PADA IBU HAMIL NY.W UMUR 32 TAHUN $G_3P_2Ab_0Ah_2$ UK 32^{+6} MINGGU DENGAN KEHAMILAN NORMAL DI PUSKESMAS IMOGIRI I

MRS TGL/JAM : 17-12-2022/ jam 08.00 WIB

S	1. Identitas Ibu — Suami Nama : Ny.W — Tn.T Usia : 32 tahun — 35 tahun Pendidikan : SMA — SMA Pekerjaan : Ibu Rumah Tangga — Karyawan Swasta Agama : Islam — Islam Alamat : Sindet RT 01, Wukirsari, Imogiri, Bantul 2. Alasan/Keluhan Kedatangan Ny.W mengatakan ingin kontrol kehamilan dan tidak ada keluhan 3. Riwayat Pernikahan Menikah 1 kali. Menikah umur 24 tahun, dengan suami sudah 8 tahun. 4. Riwayat Menstruasi Menarche umur 12 tahun. Siklus 28 hari. Teratur. Lama 5-7 hari. Sifat darah: encer. Flour albus: ada, tidak berwarna, tidak berbau. Bau khas darah. Dysmenorhoe: tidak. Banyak darah 3-4 kali ganti pembalut/hari 5. Riwayat Kehamilan ini a. Riwayat ANC HPHT 1 Mei 2022 HPL 8 Februari 2023 b. ANC sejak umur kehamilan 15 minggu. ANC di Puskesmas, PMB c. Frekuensi Trimester I 2 kali Trimester II 2 kali Trimester III 3 kali d. Pergerakan janin aktif, dalam 12 jam terakhir lebih dari 10 kali. 6. Riwayat Kesehatan a. Ny.W mengatakan tidak pernah atau tidak sedang menderita penyakit seperti IMS,HIV, ISK, kelainan bawaan, dll. b. Ny.W mengatakan bapak menderita hipertensi c. Ny.W mengatakan tidak pernah di rawat inap di rumah sakit. d. Ny.W mengatakan tidak pernah menggunakan NAPZA, tidak merokok, namun suami merokok.

7. Pola Nutrisi

		Makan	Minum
a.	Frekuensi	3 x/hari	8 x/hari
b.	Porsi	Sedang, terdiri dari 1 centong nasi, 1 potong lauk, 1 centong sayur dan 1-2 jenis buah	Gelas sedang
c.	Maca1tm	Nasi, lauk nabati dan/atau hewani, sayur dan buah	Air putih
d.	Keluhan	Tidak ada keluhan	Tidak ada keluhan

8. Pola istirahat
   Tidur siang selama 30 menit sekitar pukul 12.00-12.30 WIB dan tidur malam : ±7-8 jam sekitar pukul 21.00-05.00 WIB
9. Aktivitas Seksual
   Ny.W mengatakan melakukan hubungan seksual 1 kali seminggu.
10. Aktivitas sehari-hari
    Ny.W mengatakan kegiatan sehari-hari adalah mengerjakan pekerjaan rumah seperti menyapu, mengepel, memasak, dan mengurus anak.
11. Keadaan Psikososial
    a. Ibu, suami, dan keluarga menerima kehamilan saat ini.
    b. Pengetahuan ibu tentang kehamilan
       Kehamilan adalah masa ibu mengandung janin selama 9 bulan dan saat itu harus bisa menjaga kesehatan ibu dan janin.
    c. Dukungan keluarga
       Suami dan keluarga memberikan dukungan moril maupun materi kepada ibu dan saling membantu.
12. Persiapan/rencana persalinan
    Ibu mengatakan ingin melahirkan di Puskesmas, didampingi suami, transportasi menggunakan sepeda motor, dan menggunakan jaminan kesehatan
13. Riwayat Kehamilan, Persalinan, dan Nifas

Hamil ke-	Persalinan							Nifas	
	Tgl Lahir	UK	Jenis persalinan	Oleh	Komplikasi pada Ibu dan Bayi	JK	BB lahir	Laktasi Ya/tdk	Komplikasi
1.	2015	Aterm	Spontan	Bidan	Tidak ada	P	3100 gr	Ya	Tidak ada
2.	2018	Aterm	Spontan	Bidan	Tidak ada	P	3200 gr	Ya	Tidak ada
3.	Hamil ini								

14. Riwayat Kontrasepsi yang Digunakan

No	Jenis Alkon	Mulai memakai				Berhenti/ ganti			
		Tgl	Oleh	Tempat	Keluhan	Tgl	Oleh	Tempat	Keluhan
1.	Suntik 3 bulan	2015	Bidan	Puskesmas	Tida adak	2017	Bidan	Puskesmas	Ingin program hamil

	2.	Suntik 3 bulan	2018	Bidan	Puskesmas	Tida adak	2022	Bidan	Puskesmas	Ingin program hamil

O

1. Pemeriksaan Umum
   a. KU : Baik, kesadaran compos mentis
   b. Tanda vital : TD 105/75 mmHg, N 89 kali/menit, R 18 kali/menit, S 36,6°C
   c. BB : Sebelum hamil 58 Kg, BB sekarang 71 kg
   TB : 163 cm
   IMT : 21,8 kg/m^2 (kategori normal)
   LLA : 27 cm (tidak KEK)
2. Pemeriksaan Khusus
   a. Muka : Tidak pucat, conjungtiva tidak pucat
   b. Perut
      1) Inspeksi : Membesar memanjang, tidak ada bekas luka operasi, tidak tampak striae gravidarum
      2) Palpasi
         a) Leopold 1 : Teraba bulat, lunak, tak lenting, kesimpulan bokong janin, TFU pertengahan pusat px
         b) Leopold II : Sebelah kiri ibu teraba berbenjol-benjol, bagian kecil janin, kesimpulan ekstremitas janin, perut sebelah kanan ibu teraba keras, datar, kesimpulan punggung janin
         c) Leopold III : Teraba bulat, keras, lenting, kesimpulan kepala janin
         d) Leopold IV: Divergen, kesimpulan bagian kepala sudah masuk panggul
         Mc Donald TFU 25 cm, TBJ = (25-11)x155= 2,170 gr
      3) Auskultasi : Punctum maksimum puka, 140 kali/menit teratur
   c. Kaki : Simetris, gerakan bebas, varises: tidak ada, edema: tidak ada
3. Pemeriksaan Penunjang
   a. ANC Terpadu (09/06/2022)
      1) Hb : 14,9 gr/dL
      2) HbSAg : Negatif
      3) HIV : Negatif
      4) TPHA : Negatif
      5) GDS : 76 mg/dL
      6) Protein Urin : Negatif
      7) Gol. Darah : B+

A

Ny.A umur 32 tahun $G_3P_2Ab_0Ah_2$ UK 32^{+6} minggu dengan kehamilan normal

P

1. Memberitahu hasil pemeriksaan kepada ibu dan suami bahwa kondisinya dalam keadaan bai. Ibu mengerti dengan hasil pemeriksaan yang disampaikan.
2. Memberikan KIE mengenai ketidaknyamanan trimester III. Ibu mengerti yang disampaikan.
3. Memberikan KIE mengenai tanda bahaya kehamilan. Ibu mengerti yang disampaikan.
4. Memberikan motivasi kepada ibu untuk tetap mengkonsumsi obat yang diberikan, dan meminta suami untuk memastikan ibu sudah mengkonsumsi obatnya. Ibu dan suami bersedia saling membantu.
5. Memberikan terapi obat tablet Fe 30 buah 1x1 dan kalk 30 buah 1x1 dan memberitahu

	cara mengkonsumsi obat yang benar. Ibu mengerti dan bersedia meminumnya. 6. Memberitahu ibu untuk melakukan kunjungan ulang 1 minggu lagi atau jika ada keluhan 7. Melakukan dokumentasi asuhan yang telah dilakukan. Dokumentasi telah selesai.

CATATAN PERKEMBANGAN PEMERIKSAAN KEHAMILAN

Hari/ Tanggal, Jam	Data Subjektif	Data Objektif	Analisis	Penatalaksanaan
Senin, 09/01/2022 jam 09.00 WIB	Ibu mengatakan ingin kontrol kehamilan dan tidak ada keluhan	KU baik Kesadaran compos mentis TD 121/99 mmHg N 78x/menit R 20x/menit S 36,6^{o}C BB 71 kg Wajah tidak ada oedema Leopold I: bokong, TFU 3 jari dibawah px Leopold II: punggung kanan, ekstremitas kiri Leopold III: kepala Leopold IV: kepala sudah masuk panggul DJJ : 140 x/menit teratur TFU : 31 cm TBJ : 3,100 gr Ekstremitas : Tidak ada oedema	Ny.A umur 32 tahun $G_3P_2Ab_0Ah_2$ UK 36^{+1} minggu dengan kehamilan normal	1. Memberitahu hasil pemeriksaan bahwa saat ini ibu dan janin dalam keadaan sehat. Ibu mengerti kondisi kesehatan dirinya 2. Memberitahui ibu persiapan persalinan. Ibu sudah mempersiapkannya. 3. Mengingatkan ibu untuk mengkonsumsi obat yang diberikan secara teratur. Ibu mengerti dan bersedia melakukan anjuran yang diberikan. 4. Mengingatkan ibu tanda-tanda persalinan. Ibu masih mengingat penjelasan yang diberikan. 5. Memberitahu ibu jadwal kunjungan ulang yaitu 1 minggu lagi atau bila ada keluhan. Ibu mengerti jadwal kunjungan ulang.
Kamis, 19/01/2022 jam 09.00 WIB	Ibu mengatakan ingin kontrol	KU baik Kesadaran compos mentis TD 131/92 mmHg N 88x/menit	Ny.A umur 32 tahun $G_3P_2Ab_0Ah_2$ UK 37^{+4}	1. Memberitahu hasil pemeriksaan bahwa saat ini ibu dan janin dalam keadaan baik, namun ini mengalami tensi tinggi. Ibu mengerti kondisi kesehatan dirinya

	kehamilan dan mengatakan merasa sering kesemutan dan pusing	R 22x/menit S 36,6^{o}C BB 71 kg Wajah tidak ada oedema Leopold I: bokong, TFU 3 jari dibawah px Leopold II: punggung kanan, ekstremitas kiri Leopold III: kepala Leopold IV: kepala sudah masuk panggul DJJ : 142 x/menit teratur TFU : 32 cm TBJ : 3,255 gr Ekstremitas : Tidak ada oedema Pemeriksaan Penunjang Hb : 12,1 gr/dL Protein/Reduksi Urine: Negatif/Negatif	minggu dengan susp. preekalmpsia	2. Melakukan skrining preeklampsia dengan MAP. Hasil ibu termasuk preeklampsia 3. Menjelaskan penyebab dan risiko preeklampsia dalam kehamilan serta persalinan. Ibu mengerti 4. Memberitahu ibu bahwa ibu perlu dirujuk ke RS untuk mendapat penanganan lebih lanjut. Ibu dan keluarga memustuskan untuk dirujuk ke RSU Rajawali Citra dan menandatangani *informed consent.*
Kamis, 26/01/2023, jam 10.00 Berdasarkan buku KIA	Ibu mengatakan ingin kontrol kehamilan dan mengatakan	KU baik Kesadaran compos mentis TD 141/73 mmHg BB 74 kg Pemeriksaan USG : presentasi kepala, punggung kanan, TBJ 3000 gr	Ny.A umur 32 tahun $G_3P_2Ab_0Ah_2$ UK 38^{+6} minggu dengan preekalmpsia	1. Diberitahukan hasil pemeriksaan. Ibu mengerti kondisi kesehatan dirinya 2. Dijelaskan penyebab dan risiko dalam preeklampsia kehamilan serta persalinan. Ibu mengerti 3. Ibu diminta untuk kontrol 1 minggu lagi. Ibu bersedia melakukannya

	sering kesemutan			
Kamis, 02/02/2023, jam 11.00 Berdasarkan buku KIA	Ibu mengatakan ingin kontrol kehamilan dan mengatakan merasa pusing	KU baik Kesadaran compos mentis TD 110/82 mmHg BB 74,5 kg Pemeriksaan USG : presentasi kepala, punggung kanan, TBJ 3000 gr	Ny.A umur 32 tahun $G_3P_2Ab_0Ah_2$ UK 39^{+1} minggu dengan preekalmpsia	1. Diberitahukan hasil pemeriksaan. Ibu mengerti kondisi kesehatan dirinya 2. Dijelaskan penyebab dan risiko dalam preeklampsia kehamilan serta persalinan. Ibu mengerti 3. Dijelaskan mengenai makanan yang harus dihindari. Ibu bersedia melakukannya 4. Ibu diminta untuk kontrol 1 minggu lagi. Ibu bersedia melakukannya
Kamis, 09/02/2023, jam 10.00 WIB Berdasarkan buku KIA	Ibu mengatakan ingin kontrol kehamilan dan saat ini tidak ada keluhan	KU baik Kesadaran compos mentis TD 130/70 mmHg BB 74 kg Pemeriksaan USG : presentasi kepala, punggung kanan, TBJ 3200 gr	Ny.A umur 32 tahun $G_3P_2Ab_0Ah_2$ UK 40^{+1} minggu dengan preekalmpsia	1. Diberitahukan hasil pemeriksaan. Ibu mengerti kondisi kesehatan dirinya 2. Ibu direncanakan untuk dilakukan induksi persalinan tgl 13/02/2023 jam 18.00 WIB. Ibu dan suami bersedia 3. Ibu diminta untuk langsung ke fasilitas Kesehatan terdekat jika ada tanda-tanda persalinan. Ibu dan suami bersedia melakukannya

ASUHAN KEBIDANAN PADA IBU BERSALIN
NY.W UMUR 32 TAHUN $G_3P_2Ab_0Ah_2$ UK 40^{+5} MINGGU
DENGAN RETENSIO SISA PLASENTA
DI RSU RAJAWALI CITRA

Berdasarkan anamnesa dengan pasien dan melihat RM di RSU RC.

MRS TGL/JAM : 13-02-2023/ jam 15.00 WIB

S	1. Keluhan : Ibu mengatakan sudah ada lendir darah sejak tgl 12-02-2023 jam 08.00 WIB dan sudah kenceng-kenceng sering jam 18.00 WIB, datang ke Puskesmas jam 20.30 WIB namun belum ada pembukaan dan ibu diminta pulang. Tgl 13-02-2023 jam 00.30 WIB ibu periksa ke RSU Rajawali Citra karena sudah terasa sangat sakit. 2. Riwayat Kesejahteraan Janin Gerakan janin aktif, gerak dalam 12 jam terakhir ada lebih dari 10 gerakan 3. Pemeriksaan fisik Tekanan darah 130/80, pembukaan 1 cm 4. Penatalaksanaan Dilakukan observasi kemajuan persalinan. Jam 03.00 WIB ibu merasa pusing kemudian diberikan obat untuk menurunkan tekanan darah. Jam 05.00 WIB pembukaan menjadi 5 cm, merasa ingin mengejan terus-menerus dan selaput ketuban masih belum pecah. Kemudian dibantu bidan untuk memecah selaput ketuban dan pembukaan langsung lengkap, bayi lahir secara normal jam 05.50 WIB. Ada robekan jalan lahir dan dijahit dengan anestesi. Bayi lahir BB 3,695 gram dan PB 50,5 cm. Plasenta lahir, kemudian dipasang KB IUD pasca salin sesuai permintaan ibu.

Catatan Perkembangan (Tgl 13-02-2023, jam 08.00 WIB)

S	1. Keluhan : Ibu mengatakan merasa kontraksi seperti pembukaan 2 cm. 2. Pemeriksaan Penunjang Pemeriksaan USG : Tampak ada sisa plasenta 3. Penatalaksanaan Ibu direncanakan kuret tgl 14/02/2023 jam 13.00 WIB untuk mengeluarkan sisa plasenta yang masih tertinggal. Setelah dilakukan kuret dan dilakukan observasi semalam, tgl 15/02/2023 ibu diperbolehkan pulang.

ASUHAN KEBIDANAN PADA BAYI BARU LAHIR
BY. Ny. W UMUR 1 JAM CUKUP BULAN SESUAI MASA KEHAMILAN
DI RSU RAJAWALI CITRA

Tangal/Jam : 13-02-2023 jam 06.50 WIB

Berdasarkan buku KIA dan anamnesa dengan ibu

S

1. Identitas Anak
   Nama : By.Ny.W
   Tanggal lahir : 13-02-2023
   Umur : 1 jam
   Jenis kelamin : Perempuan
2. Riwayat Intranatal
   Lahir tanggal 13-02-2023 jam 05.50 WIB
   Jenis persalinan : Spontan
   Penolong : Bidan di RSU Rajawali Citra
   Lama persalinan : Kala I 4 jam 30 menit
   Kala II 25 menit
   Kala III 15 menit
   Kala IV 2 jam
3. Keadaan bayi baru lahir
   BB/ PB Lahir : 3,695 gr / 50,5 cm

No	Kriteria	1 menit	5 menit	10 menit
1	Denyut Jantung	2	2	2
2	Usaha Nafas	2	2	2
3	Tonus Otot	2	2	2
4	Reflek	1	2	2
5	Warna kulit	2	2	2
Total		9	10	10

   Nilai APGAR : 1menit/ 5menit/ 10menit : 9//10/10
   Caput succedaneum : tidak ada
   Cephal hematom : tidak ada
   Cacat bawaan : tidak ada
4. Keluhan
   Bayi lahir spontan, sehat, menangis kuat, kulit kemerahan, gerakan aktif

1. Pemeriksaan umum
   a. KU : Baik
   b. Kesadaran : Compos mentis
   c. Suhu : 36,5°C
   d. BB : 3,695 gr
   e. PB : 50,5 cm
   f. LK : 33 cm
   g. LD : 34 cm
   h. LLA : 12 cm

	i. RR : 44 x/m j. Nadi : 128 x/m 2. Pemeriksaan fisik a. Kepala : simetris, tidak terdapat benjolan, tidak terdapat caput succedaneum dan cepal hematoma b. Mata : bentuk simetris, konjungtiva tidak anemis, sklera tidak ikterik c. Hidung : simetris, tidak terdapat kotoran, tidak terdapat pernafasan cuping hidung d. Mulut : tidak tampak labioskizis dan labiopalatoskizis, lidah bersih e. Leher : tidak terdapat pembesaran kelenjar tiroid, limfe, dan vena jugularis f. Dada : simetris, tidak ada retraksi tarikan dinding dada kedalam g. Abdomen : simetris, tidak terdapat benjolan abnormal, tali pusar massih basah h. Punggung : tidak ada spina bifida i. Genetalia : labia mayora menutupi labia minora j. Anus : berlubang k. Ekstremitas 1) Atas : simetris, tidak terdapat sindaktili atau polidaktili, jari-jari lengkap, ektremitas tidak kebiruan dan tidak ikterik. 2) Bawah : simetris, tidak terdapat sindaktili atau polidaktili, jari-jari lengkap, ektremitas, tidak kebiruan dan tidak ikterik. l. Reflek 1) Moro : + (bayi terkejut) 2) Rooting : + (bayi mengikuti arah sentuhan) 3) Walking : + (bayi menggerakkan kakinya) 4) Graphs : + (bayi bisa menggenggam) 5) Sucking : + (bayi menghisap dengan baik) 6) Tonic neck : + (bayi mampu menolehkan kepalanya) m. Eliminasi : miksi (+), mekonium (+)
A	By. Ny.E umur 1 jam cukup bulan sesuai masa kehamilan normal
P	1. Diberitahu hasil pemeriksaan kepada orangtua bahwa kondisi bayi baik. Orangtua mengerti kondisi anaknya 2. Dilakukan observasi KU dan Vital Sign. Hasil pemeriksaan dalam batas normal 3. Ibu diberitahu cara menjaga kehangatan bayi dengan mengganti pakaian bayi bila basah atau kotor. Suhu bayi terjaga tidak hipotermi 4. Ibu diberitahu untuk memberikan ASI sesering mungkin pada bayi minimal tiap 2 jam atau sesuai kebutuhan dan membantu ibu menyusui bayinya. Ibu mengerti dan bersedia memberikan ASI sesering mungkin 5. Dilakukan observasi BAB dan BAK. Bayi sudah BAB dan BAK 6. Ibu diberitahu bahwa bayinya akan dimandikan setelah 6 jam post partum. Keluarga mengerti dan bersedia 7. Dilakukan injeksi vitamin K 1 mg secara IM pada paha kiri 1/3 bagian luar atas dan salep mata eritromycin 0,5 % sebanyak 1 tetes pada mata kanan dan mata kiri segera setelah bayi lahir. Sudah diberikan 8. Ibu diberitahu cara mengganti popok apabila bayi BAB dan BAK tidak boleh diberi bedak pada daerah kelamin memberitahu cara merawat tali pusat yaitu dengan cara dibiarkan kering dan bersih. Keluarga mengerti cara merawat bayi.

	9. Ibu diberitahu mengenai tanda bahaya bayi baru lahir diantaranya yaitu merintih, demam, kulit berwwarna kuning, tidak mau menyusu, dan muntah. Apabila terdapat salah satu dari tanda tersebut maka ibu harus segera melaporkan ke bidan. Ibu mengerti tanda bahaya bayi baru lahir.

CATATAN PERKEMBANGAN NEONATUS

Hari, Tanggal/ Jam	Data Subjektif	Data Objektif	Analisis	Penatalaksanaan
KN I Senin, 13/02/2023, 14.00 WIB	Ibu mengatakan bayinya dalam kondisi sehat, tali pusat dalam kondisi bersih, tidak mengalami ikterik dan diare, sudah bisa menyusu dan sudah BAB serta BAK	Berdasarkan data subjektif: KU baik Kesadaran compos mentis S 36,8 °C	By.Ny.W umur 8 jam cukup bulan sesuai masa kehamilan	1. Memberitahu hasil pemeriksaan kepada ibu bahwa bayinya dalam keadaan baik 2. Dilakukan cap kaki kanan dan kiri bayi untuk bukti kelahiran bayi dan kelengkapan rekam medis bayi baru lahir dan buku KIA. 3. Diberikan suntikan imunisasi Hb0 4. Disampaikan tentang ASI ekslusif dan teknik menyusui yang benar.
KN II Rabu, 15/02/2023, 10.00 WIB	Ibu mengatakan bayinya dalam kondisi baik, tidak kuning, tidak demam	KU baik, Kesadaran compos mentis BB 3700 gr PB 50,5 cm S 36,5 °C Tali pusat kering, tidak ada tanda infeksi Tidak ada tanda ikterik	By.Ny.W umur 3 hari normal	1. Memberitahu hasil pemeriksaan kepada ibu bahwa bayinya dalam keadaan baik 2. Mengingatkan ibu untuk menyusui bayinya sesering mungkin atau minimal 2 jam sekali untuk mengatasi kuning yang dialami bayinya, memenuhi nutrisi bayi dan menambah asupan makanan sayur-sayuran hijau agar membantu produksi ASI. Ibu bersedia melakukannya. 3. Mengingatkan ibu untuk menjemur bayi di bawah sinar matahari selama 15-30 menit setiap hari pada rentang pukul 07.00-09.00 WIB dengan menutup

				mata dan bagian alat kelamin bayi serta menghindari posisi yang membuat bayi melihat langsung ke arah matahari yang dapat merusak matanya. Ibu sudah mencoba melakukannya. 4. Memberi konseling ibu untuk menjaga kehangatan bayinya dengan membedong bayi dan memakaikan topi serta segera mengganti popok bayi apabila BAB/BAK. Ibu mengerti dengan penjelasan yang diberikan.
KN III Rabu, 22/02/2023, 08.00 WIB	Ibu mengatakan bayinya sehat, menyusu kuat	KU baik, Kesadaran compos mentis BB 3780 gr PB 51 cm S 36,8 °C Tali pusat sudah lepas Tidak ada tanda ikterik	By.Ny.W umur 10 hari normal	1. Memberi konseling ibu untuk menjaga kehangatan bayinya dengan membedong bayi dan memakaikan topi serta segera mengganti popok bayi apabila BAB/BAK. Ibu mengerti dengan penjelasan yang diberikan. 2. Memberikan ibu KIE mengenai ASI ekslusif. Ibu mengerti mengenai asi ekslusif 3. Memberitahu ibu untuk selalu mencuci tangan sebelum memegang atau memberikan ASI pada bayinya agar bayi terhindar dari virus penyakit. Ibu mengerti dengan penjelasan bidan. 4. Mengingatkan ibu untuk melakukan imunisasi BCG pada bayinya. Ibu bersedia melakukannya.

CATATAN PERKEMBANGAN PEMERIKSAAN NIFAS

Hari, Tanggal/ Jam	Data Subjektif	Data Objektif	Analisis	Penatalaksanaan
KF I Senin, 13/02/2023, 14.00 WIB	Ibu mengatakan keadaan saat ini baik dan sehat. Ibu sudah mengonsumsi Vitamin A, sudah BAK dan belum BAB	Berdasarkan data subjektif: KU baik Kesadaran compos mentis TD 110/70 mmHg N 80 kali/menit R 22 kali/menit Suhu 36,5 °C BB 71 kg Kontraksi uterus keras TFU 2 jari dibawah pusat Perdarahan pervaginam dalam batas normal, lochea rubra, bekas jahitan masih basah, tidak ada tanda infeksi Tidak ada varices atau bengkak dikaki	Ny.A usia 32 tahun $P_3Ab_0Ah_3$ postpartum 8 jam normal	1. Menyampaikan hasil pemeriksaan kepada ibu bahwa ibu dalam keadaan baik. Ibu mengerti 2. Memberikan KIE untuk memberikan ASI eksklusif pada bayinya. Ibu bersedia melakukannya 3. Memberikan KIE mengenai teknik menyusui yang benar. Ibu dapat mempraktikkannya dengan baik 4. Memberikan KIE untuk meningkatkan pemenuhan kebutuhan nutisi dan memenuhi kebutuhan cairan dengan mengkonsumsi air putih sebanyak 2-3 liter/hari. Ibu bersedia melakukannya 5. Memberikan KIE mengenai tanda bahaya masa nifas. Ibu mengerti yang disampaikan.

KF II Rabu, 17/02/2023, 10.00 WIB	Ibu mengatakan tidak ada keluhan	KU baik Kesadaran compos mentis TD 110/87 mmHg N 80 kali/menit R 22 kali/menit S 36,2^{o}C BB 71 kg Wajah tidak pucat, tidak ada edema Payudara simetris, putting menonjol dan lecet pada bagian kiri, ASI+ Abdomen TFU pertengahan sympisis pusat, kontraksi keras Vulva bersih, lochea sanguilenta, jahitan masih basah, tidak ada tanda infeksi, Ekstremitas tidak ada tromboemboli	Ny.A umur 32 tahun $P_3Ab_0Ah_3$ postpartum hari ke 3 normal	1. Memberitahu hasil pemeriksaan bahwa saat ini ibu dalam keadaan baik. Ibu mengerti dan merasa tenang dengan kondisinya. 2. Memberitahukan ibu untuk mengusap puting susu yang lecet dengan ASI setelah menyusui bayinya, dan dibiarkan kering terlebih dahulu sebelum menggunakan bra kembali. Meminta ibu untuk tetap menyusui bayinya setiap 2 jam sekali atau jika bayi menginginkannya. Ibu mengerti dan bersedia melakukannya. 3. Memberi ibu KIE mengenai *personal hygiene.* Membersihkan bagian kewanitaan dengan air bersih dan sabun kemudian dikeringkan menggunakan handuk bersih agar tidak lembab. Jangan takut untuk membersihkan luka jahitan agar tidak terjadi infeksi. Ibu bersedia melakukan anjuran tersebut. 4. Memberi ibu KIE mengenai nutrisi. Menganjurkan ibu untuk mengonsumsi makanan tinggi protein dan zat gizi agar pemulihan tubuh ibu berlangsung cepat dan produksi ASI melimpah. Menganjurkan ibu untuk minum minimal 3 liter per hari agar kebutuhan cairan ibu tercukupi. Ibu mengerti dan berusaha mengukuti anjuran yang diberikan.

				5. Menganjurkan ibu untuk menyusui anaknya secara *on demand* atau tidak terjadwal. Ibu bersedia menyusui bayinya sesering mungkin 6. Memberi KIE ibu untuk istirahat yang cukup agar produksi ASI lancar. Ibu mengerti dengan penjelasan. 7. Memberikan KIE dan mengajarkan ibu senam nifas. Ibu bersedia melakukannya. 8. Menganjurkan suami ibu untuk ikut serta dalam mengasuh dan merawat anak secara bergantian agar ibu tidak kelelahan. Suami bersedia dan sanggup untuk membantu merawat bayi ketika tidak sedang bekerja. 9. Memberi motivasi kepada ibu untuk memberikan ASI ekslusif selama 6 bulan kepada bayinya. Ibu bersedia untuk menyusui anaknya secara ekslusif selama 6 bulan.
KF III Rabu, 22/02/2023, 09.00 WIB	Ibu mengatakan saat ini keadaannya baik dan sehat.	KU baik Kesadaran compos mentis TD 110/87 mmHg N 80 kali/menit R 22 kali/menit S 36,2^{o}C BB 69 kg Wajah tidak pucat, tidak ada edema	Ny.A umur 32 tahun $P_3Ab_0Ah_3$ postpartum hari ke 10 normal	1. Memberitahu ibu bahwa secara umum keadaan ibu baik, pemulihan tubuh ibu berjalan dengan baik. Ibu merasa lega. 2. Menganjurkan suami ibu untuk ikut serta dalam mengasuh dan merawat anak secara bergantian agar ibu tidak kelelahan. Suami bersedia dan sanggup untuk membantu merawat bayi ketika tidak sedang bekerja. 3. Memberi ibu KIE mengenai *personal hygiene.* Membersihkan bagian kewanitaan dengan air bersih dan sabun kemudian dikeringkan

		Payudara simetris, putting menonjol dan tidak lecet, ASI+ Abdomen TFU tidak teraba Vulva bersih, lochea serosa, jahitan sudah kering, menyatu, tidak ada tanda infeksi, Ekstremitas tidak ada tromboemboli		menggunakan handuk bersih agar tidak lembab. Jangan takut untuk membersihkan luka jahitan agar tidak terjadi infeksi. Ibu bersedia melakukan anjuran tersebut. 4. Memberi ibu KIE mengenai nutrisi. Menganjurkan ibu untuk mengonsumsi makanan tinggi protein dan zat gizi agar pemulihan tubuh ibu berlangsung cepat dan produksi ASI melimpah. Menganjurkan ibu untuk minum minimal 3 liter per hari agar kebutuhan cairan ibu tercukupi. Ibu mengerti dan berusaha mengukuti anjuran yang diberikan. 5. Menganjurkan ibu untuk menyusui anaknya secara *on demand* atau tidak terjadwal. Ibu bersedia menyusui bayinya sesering mungkin. 6. Memberi KIE ibu untuk istirahat yang cukup agar produksi ASI lancar. Ibu mengerti dengan penjelasan. 7. Menganjurkan suami ibu untuk ikut serta dalam mengasuh dan merawat anak secara bergantian agar ibu tidak kelelahan. Suami bersedia dan sanggup untuk membantu merawat bayi ketika tidak sedang bekerja. 8. Memberi motivasi kepada ibu untuk memberikan ASI ekslusif selama 6 bulan kepada bayinya. Ibu bersedia untuk menyusui anaknya secara ekslusif selama 6 bulan.

KF IV Rabu, 22/03/2023, 09.00 WIB	Ibu mengatakan saat ini tidak ada keluhan dan hanya memberikan ASI saja untuk bayinya.	KU baik Kesadaran compos mentis TD 120/80 mmHg N 86 kali/menit R 22 kali/menit S 36,2^{o}C BB 66 kg Wajah tidak pucat, tidak ada edema Payudara simetris, putting menonjol dan tidak lecet, ASI+ Abdomen TFU tidak teraba Vulva bersih, bekas jahitan sudah tidak terlihat, lochea alba, tidak ada tanda infeksi Ekstremitas tidak ada tromboemboli	Ny.A usia 32 tahun $P_3Ab_0Ah_3$ postpartum minggu ke 6 normal	1. Memotivasi ibu untuk selalu memberikan ASI ekslusif pada bayinya. Ibu setuju untuk ASI eksklusif. 2. Mengingatkan efek samping penggunaan KB IUD. Ibu mengerti yang disampaikan. 3. Memberitahu ibu untuk menjaga pola personal hygiene, dengan membersihkan alat kelamin saat mandi, setelah BAK, dan BAB, menggunakan celana yang dapat menyerap keringat. Ibu bersedia melakukannya 4. Menganjurkan ibu untuk melakukan senam nifas agar ibu segera pulih. Ibu bersedia

ASUHAN KEBIDANAN PADA AKSEPTOR KB
NY.W UMUR 32 TAHUN $P_3Ab_0Ah_3$ AKSEPTOR KB IUD
DI WILAYAH PUSKESMAS

MRS TGL/JAM : 31-03-2023/ jam 10.00 WIB

S	Ibu mengatakan merasa benang IUD keluar saat haid
O	1. KU : Baik, kesadaran compos mentis 2. Tanda vital a. Tekanan Darah : 120/80 mmHg b. Nadi : 86 kali/menit c. Respirasi : 22 kali/menit d. Suhu : 36,2°C 3. BB : 66 kg 4. Kepala dan Leher a. Wajah : Tidak pucat, tidak ada edema b. Mata : Konjungtivas merah muda, sklera putih c. Mulut : Bibir lembab, tidak sariawan 5. Abdomen : Tidak ada bekas luka jahitan, tidak teraba massa, tidak ada nyeri tekan 6. Ekstremitas : Simetris, tidak ada varices, tidak ada edema 7. Genetalia Luar : Bersih, tidak ada tanda infeksi, tidak ada perdarahan 8. Anus : Tidak ada hemoroid
A	Ny.W umur 32 tahun $P_3Ab_0Ah_3$ akseptor KB IUD
P	1. Memberitahu ibu hasil pemeriksaan umum kepada ibu bahwa ibu dalam keadaan baik. Ibu mengerti hasil pemeriksaan yang disampaikan 2. Menjelaskan mengenai keluhan dan efek samping penggunaan KB IUD. Ibu mengerti yang dijelaskan 3. Memberikan dukungan atau support agar ibu tidak khawatir atau takut. Ibu terlihat lebih tenang. 4. Menganjurkan kepada ibu untuk control IUD ke PMB atau Puskesmas jika keluhan masih dirasakan dan mengganggu. Ibu bersedia 5. Mendokumentasikan asuhan yang telah diberikan. Dokumentasi telah selesai dilakukan.

Lampiran 2. Daftar Hadir Pasien

Lampiran 3. *Informed Consent*

INFORMED CONSENT (SURAT PERSETUJUAN)

Yang bertanda tangan di bawah ini:

Nama : Widya Oktaviani

Tempat/Tanggal Lahir : Yk, 2-10-1990

Alamat : Gindet, Wukirsari

Bersama ini menyatakan kesediaan sebagai subjek dalam praktik Continuity of Care (COC) pada mahasiswa Prodi Pendidikan Profesi Bidan T.A. 2020/2021. Saya telah menerima penjelasan sebagai berikut:

1. Setiap tindakan yang dipilih bertujuan untuk memberikan asuhan kebidanan dalam rangka meningkatkan dan mempertahankan kesehatan fisik, mental ibu dan bayi. Namun demikian, setiap tindakan mempunyai risiko, baik yang telah diduga maupun yang tidak diduga sebelumnya.
2. Pemberi asuhan telah menjelaskan bahwa ia akan berusaha sebaik mungkin untuk melakukan asuhan kebidanan dan menghindarkan kemungkinan terjadinya risiko agar diperoleh hasil yang optimal.
3. Semua penjelasan tersebut di atas sudah saya pahami dan dijelaskan dengan kalimat yang jelas, sehingga saya mengerti arti asuhan dan tindakan yang diberikan kepada saya. Dengan demikian terdapat kesepahaman antara pasien dan pemberi asuhan untuk mencegah timbulnya masalah hukum di kemudian hari.

Demikian surat persetujuan ini saya buat tanpa paksaan dari pihak manapun dan agar dipergunakan sebagaimana mestinya.

Yogyakarta, ...

Mahasiswa	Klien
Wahyu Diana R	Widya Oktaviani

Lampiran 4. Surat Keterangan telah Menyelesaikan COC

SURAT KETERANGAN

Yang bertanda tangan di bawah ini:

Nama Pembimbing Klinik : Sumaryati, S.ST. Keb, S. Pd
Instansi : Puskesmas/~~PMB~~ Imogiri I

Dengan ini menerangkan bahwa:

Nama Mahasiswa : Wahyu Diana Rahmawati
NIM : P07124522023
Prodi : Pendidikan Profesi Bidan
Jurusan : Kebidanan Poltekkes Kemenkes Yogyakarta

Telah selesai melakukan asuhan kebidanan berkesinambungan dalam rangka praktik kebidanan holistik Continuity of Care (COC)
Asuhan dilaksanakan pada tanggal 12/12 22 sampai dengan 21/3 23
Judul asuhan: Asuhan Kebidanan Berkesinambungan Pada Ny. W usia 32 tahun G3 P2 Ab0 Ah2 Dengan Pre-eklampsia dan Retensio sita Plasenta di Puskesmas Imogiri I

Demikian surat keterangan ini dibuat dengan sesungguhnya untuk dipergunakan sebagaimana mestinya.

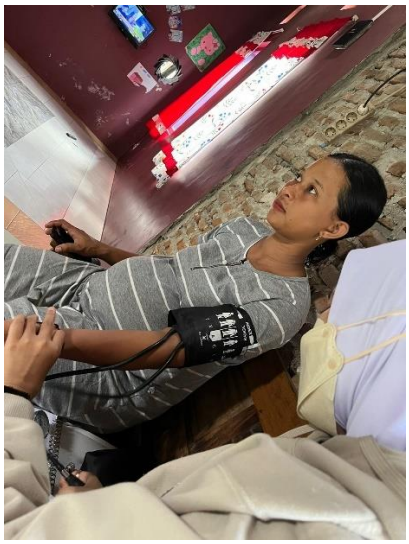
Yogyakarta, ...
Bidan (Pembimbing Klinik)

PEMERINTAH KABUPATEN BANTUL DINAS KESEHATAN UPTD PUSKESMAS IMOGIRI I

Sumaryati, S.ST. Keb, S.Pd

Lampiran 5. Dokumentasi Kegiatan

Pendampingan CI lahan



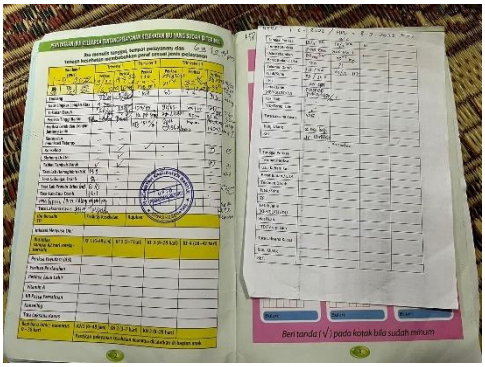
Anamnesa ANC I

Pemeriksaan Kehamilan

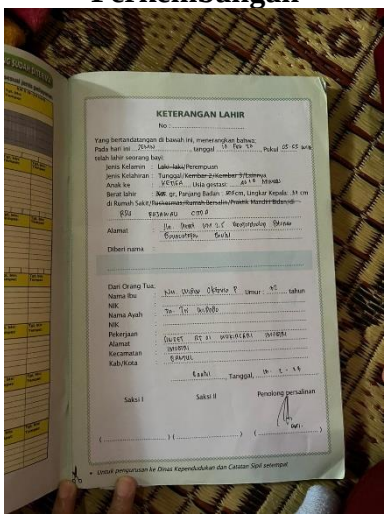
Kunjungan Nifas

Kunjungan Neonatus

Pemberian KIE SDIDTK untuk Perkembangan



Dokumentasi Pemeriksaan ANC



Catatan Persalinan

Bersama keluarga Tn. T dan Ny. W

By. M

Lampiran 6. Jurnal Referensi

HYPERTENSION IN PREGNANCY
https://doi.org/10.1080/10641955.2020.1754851

Magnesium intoxication in women with preeclampsia with severe features treated with magnesium sulfate

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ABSTRACT

Objective: To evaluate the maternal-neonatal outcome in magnesium (Mg)-intoxicated women with preeclampsia with severe features (PESF) treated with magnesium sulfate ($MgSO_4$).

Methods: A total of 19 Mg intoxicated PESF women (cases) were compared with 166 PESF women without signs of intoxication (controls).

Results: Mg serum levels of cases was higher compared to control group (12.36 ± 3.54 mg/dl versus 2.69 ± 0.83 mg/dl). 3 women died and 3 had major maternal morbidity in cases group compared with zero in the control group (P = 0.009). Mg intoxication was also significantly associated with perinatal deaths and low Apgar scores at 1 and 5 minutes.

Conclusion: Mg intoxication is associated with a increased risk of maternal and perinatal mortality and morbidity.

ARTICLE HISTORY
Received 13 November 2019
Accepted 7 April 2020

KEYWORDS
Magnesium intoxication; hypermagnesemia; magnesium sulfate; preeclampsia with severe features

Introduction

Preeclampsia (PE) is a life-threatening syndrome in pregnancy characterized by the new onset of hypertension after 20 weeks of gestational age and accompanied by proteinuria or other signs of organ involvement (1). PE is one of the main problems in pregnancy, causing maternal mortality and morbidity in low and middle-income countries (Duley et al., 1992). About 50,000–63,000 women die each year of PE/eclampsia. Indonesia, the fourth most populous country in the world with a population of 267 million, is a middle-income country with PE incidence of 5-7%. The maternal (2.2%) and perinatal mortality rate (12%) of PE are still high (2). A large segment of the Indonesian population still faces poverty, has lack of access to health care, and often receives inadequate treatment in primary health-care centers. The wrong financial incentives under the current Indonesian universal health coverage system are partially to blame for too late referrals (3).

Magnesium sulfate ($MgSO_4$) is recommended unanimously by all major guidelines as a first-choice agent to prevent eclamptic seizures and is used worldwide (4). The Magpie trial, the large international multicenter randomized controlled trial (RCT), reported that the use of $MgSO_4$ reduces the risk of eclampsia about 58% in women with PE compared with PE women receiving placebo (5). $MgSO_4$ as an anticonvulsant agent works through multiple mechanisms: inhibits seizure excitability in the cerebral cortex, inhibits the N-methyl-D-aspartate receptor in the hippocampus, and calcium metabolism in the neuromuscular junction. $MgSO_4$ also works as a potent vasodilator, especially in the cerebral vasculature, potentially reducing brain ischemia-hypoxia in preeclamptic women (6). Although $MgSO_4$ has been proven to be effective in preventing eclampsia, its use still contains a small but definitive risk of magnesium intoxication or hypermagnesemia (7–9).

Mg intoxication is clinically evident when serum Mg levels exceed 12 mg/dL (hypermagnesemia), which almost exclusively occurs in PE women with marked renal involvement or in women receiving higher $MgSO_4$ infusion rates (10). The main symptoms of Mg intoxication are the result of its general CNS depressant effects, peripheral depression affecting muscle contractility, and central neuromuscular transmission blockade. Clinical manifestation of Mg

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intoxication seldom occurs until magnesium levels reach a total dosage beyond 12 mg/dL in maternal blood. Clinical manifestations of Mg intoxication include general weakness, double vision, low blood pressure, loss of conscious and respiratory distress. The lethal manifestation, cardiac arrest, may happen if Mg concentration rises above 30 mg/dL (8,11,12).

Hypertension in pregnancy, especially PESF is in the top three diagnosis of the sickest high-risk obstetrics cases in Dr. Soetomo General Academic Hospital, the main tertiary referral hospital in Surabaya, Indonesia (13,14). Intravenous $MgSO_4$ is administrated routinely in PESF without measurements of Mg levels unless there are clinical indications (suspicion Mg intoxication) due to lack of adequate hospital funding under the Indonesian national insurance system.

In this study, we evaluated the incidence of Mg intoxication in women with PESF receiving $MgSO_4$ and investigated its association with adverse maternal and perinatal outcomes.

Material and methods

This study was conducted in Dr. Soetomo Hospital, the major tertiary referral center in East-Java, Indonesia, from January 2014 – December 2018; all women with PESF receiving Mg with clinical signs and symptoms of Mg intoxication and confirmed hypermagnesemia (cases n = 19) were compared to 166 PESF patients (8 controls per case) also treated with Mg but without signs of Mg intoxication (control group). The historical control group was recruited randomly with 33–34 patients each year to achieve a balanced distribution (2014–2018). Since Mg levels are not routinely checked in our hospital in PESF patients receiving $MgSO_4$, Mg levels in this study were only measured in women with signs or symptoms of Mg intoxication. In the control group, 24 random women out the 166 also had a Mg level measured. Mg level was measured using the Calmagite Colorimetric method (Hardness reagen set).

PE was defined using ISSHP classification: hypertension developing after 20 weeks gestation and the existence of one or more of the following: proteinuria, other maternal organ dysfunction (renal insufficiency, liver involvement, neurological complications, hematological complications), and uteroplacental dysfunction. HELLP syndrome was defined as a combination of hemolysis (lactic dehydrogenase >1000 U/L, schistocytes in blood smear), elevated liver enzymes, and thrombocytopenia (platelet count < 100.000 u/L) in PE women. PESF was defined as PE with any of the following findings: systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg on two occasions at least 4 hours apart, thrombocytopenia, elevated liver enzymes (AST > 45 μ/L, ALT > 35 μ/L), progressive renal insufficiency (BUN > 20 mg/dL, serum kreatinin > 1.1 mg/dL), pulmonary edema, and cerebral or visual disturbances. Pulmonary edema was defined based on symptoms of shortness of breath/difficulty breathing, physical examination, and confirmed with a chest X-ray (15). Hypertensive crisis was defined as systolic blood pressure more than 180 mmHg and/or diastolic blood pressure more than 120 mmHg (1,4,16,17).

Every patients with PESF in our hospital received $MgSO_4$, using the Zuspan regimen consisting of a loading dose 4 g in 20 ml (20% solution) administered iv over 15–20 minutes, followed by a maintenance dose of 1 g/hour iv infusion using syringe pump from admission until 12 hours or 24 hours after delivery in case of eclampsia (18). In preterm PESF women managed conservatively, $MgSO_4$ is administered the first 24 hours following admission. In these women, $MgSO_4$ is discontinued during their observation period and started again at the time of delivery. On the other hand, the regimen mostly used in primary health-care centers consists of a modified Pritchard scheme; loading dose of 4 gram 20% iv $MgSO_4$ in 10–15 minutes and 10 gram IM (5 gram in each buttock), followed by maintenance dose 5 gram IM $MgSO_4$ in alternate buttock for every 6 hours (19).

Cases of Mg intoxication were identified as women who received $MgSO_4$ treatment and had documented clinical signs of magnesium intoxication in addition to serum magnesium levels >12 mg/dL. Clinical signs and symptoms included muscles weakness, loss of deep tendon reflexes, respiratory paralysis, ECG changes (prolonged PR interval and widened QRS complex), SA or AV node block, loss of consciousness or cardiac arrest.

The primary outcomes of the study were maternal and perinatal outcomes among the 19 cases compared with the 166 controls. The maternal parameters evaluated included maternal age, body mass index (BMI), parity, referral origin, antenatal history, PE type. Maternal outcomes included mode of delivery, gestational age at delivery, laboratory results, maternal complications, and maternal death. PE complications included any of the following: eclampsia, HELLP syndrome, pulmonary edema, hypertensive crisis, acute kidney injury. The definition of maternal death in this study was any death during the treatment in hospital, and not necessarily a direct effect of Mg intoxication. Perinatal outcomes included fetal sex, birth weight, Apgar scores (minutes 1 & 5), SGA (<10th population birth weight centile), and perinatal death.

The results were analyzed using chi-square test, independent t-test, Mann Whitney test, and Fisher exact test where appropriate. Statistical measurement was performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Released 2017.

Results

Incidence of Mg intoxication in women with PESF

The incidence of PESF during the period 2014–2018 was 1743 cases out of a total of 6823 total deliveries (25.54%); Mg intoxication was diagnosed in 19 patients (1.09%). The annual incidence of Mg intoxication over this 5-year period varied between 0.6% and 1.5%.

Maternal characteristics

The overall characteristics between the two groups were quite similar (Table 1) except the origin of the cases. All Mg intoxicated cases were referred from other hospitals or primary health-care centers compared with 80.2% in the control group: 19.8% women in the control group had regular antenatal care in our hospital (booked case). Twelve (63.2%) cases with Mg intoxication were referred from distant rural areas. There was no significant difference in maternal age, BMI, parity, and PE type between both groups.

Maternal outcomes

The clinical manifestations of Mg intoxication were varied: 42.1% of women demonstrated muscle weakness (loss of patellar reflex), 10.5% respiratory depression, and 42.1% loss of consciousness. The maternal outcomes of cases versus controls are presented in Table 2. The mode of delivery between both groups was not different, most patients in both groups were delivered by cesarean section.

The rate of maternal mortality and severe morbidities was higher among cases compared with the controls; 14 out of the 19 cases (73%) had a major complication, including 3 maternal deaths compared with 30.7% major complication rate in the control group (OR 2.85; 95% CI 2.12–3.82). Eclampsia and HELLP syndrome were the main complications found in the case group. Interestingly we found no pulmonary edema among the cases compared with 13 (7.8%) in the control group.

Importantly, the three maternal deaths were not directly caused by the actual Mg intoxication but were related to other complications such as septic shock, thyroid crisis, and intracerebral hemorrhage. Laboratory manifestations reflecting disease severity were significantly worse in the case group (protein urine, LDH, ALT, AST, BUN, SK, and Albumin).

A subgroup analysis was performed in PESF control women who had their serum Mg levels measured (Table 3). The Mg level among the cases was markedly elevated compared with controls (12.36 ± 3.45 versus 2.69 ± 0.83 mg/dL; $p < 0.001$). The minimum and maximum level of both groups were as follows: cases (8.9–25.6 mg/dL) versus controls (1.5–4.3 mg/dL). In addition, we found a significant difference in the total Mg dose, length, and method of Mg administration between the groups. A significantly higher proportion of cases received >24 g of Mg, and had Mg administered for >24 hours, and had Mg administered by intramuscular injection. As high as 21.1% of cases had oliguria.

Perinatal outcomes

Maternal Mg intoxication had a significant association with worse perinatal outcomes: lower 1 and 5 minute

Table 1. Maternal characteristics of PESF patients treated with Mg with (cases) and without Mg intoxication (controls).

	Cases n = 19	Controls n = 166	p value	OR (95% CI)
Maternal Age	28.83 + 6.191	31.96 + 6.769	0.415	NA
BMI	30.9875 + 8.694	30.6698 + 7.210	0.973	NA
Parity				
Primipara	4 (21.2%)	51 (31.1%)	0.349	NA
Multipara	15 (78.9%)	115 (68.9%)		
Referral origin				
Country	12 (63.2%)	42 (25.5%)	0.001*	5.02
The City	7 (36.8%)	124 (74.5%)		(1.85–13.59)
Booked Case				
No	19 (100%)	134 (80.2%)	0.005*	9.72
Yes	0	32 (19.8%)		(0.57–165.03)
PE type				
Early onset PE	14 (73.6%)	104 (62.7%)	0.314	NA
Late onset PE	5 (26.4%)	62 (37.3%)		

Table 2. Maternal outcomes of cases versus controls.

	Cases n = 19	Controls n = 166	*p* value	OR (95% CI)
GA at delivery	31.63 ± 3.51	33.81 ± 3.33	0.014*	NA
Mode of delivery				
CS	11 (57.9%)	110 (66.3%)	0.473	NA
Vaginal delivery	8 (42.1%)	56 (33.7%)		
Complication				
Yes	14 (73.7%)	51 (30.7%)	0.0002*	2.86
No	5 (26.3%)	115 (69.3%)		(2.12–3.82)
Complication type	14	51	0.0113*	NA
Eclampsia	6 (42.9%)	9 (17.6%)		
HELLP Syndrome	3 (21.4%)	11 (21.6%)		
Pulmonary edema	0	13 (25.5%)		
IUGR	1 (7.1%)	4 (7.8%)		
IUFD	3 (21.5%)	1 (2%)		
Multiple complication	0	9 (17.6%)		
Emergency Hypertension	0	1 (2%)		
Acute Kidney Injury	1 (7.1%)	3 (5,9%)		
Maternal death				
Yes	3 (15.8%)	0	0.009*	
No	16 (84.2%)	166 (100%)		
BUN	33.75 + 20.56	10.93 + 8.84	0.000*	
Serum Creatinine	2.61 + 1.68	0.65 + 0.07	0.000*	
Serum Albumin	2.64 + 0.38	2.58 + 0.55	0.000*	
ALT	59.58 + 94.79	43.35 + 12.72	0.057*	
AST	96.68 + 203.56	21.25 + 3.8	0.000*	
Protein Urine			0.024*	NA
(-)	0	3 (1.8%)		
+1	1 (5.3%)	20 (12.1%)		
+2	1 (5.3%)	56 (33.9%)		
+3	10 (52.6%)	55 (33.3%)		
≥4	7 (36.8%)	31 (18.8%)		

Table 3. Subgroup analysis of cases vs controls group.

	Cases n = 19	Controls n = 24	*p* value	OR (95% CI)
Mg level (gl	12.36 ± 3.45	2.69 ± 0.83	<0.001*	NA
Urine output (ml/hour)				
<30	4 (21.1%)	0	0.031*	2.6
≥30	15 (78.9%)	24 (100%)		(0.9–7.2)
Methods of $MgSO_4$ administration				
im	10 (52.6%)	5 (20.8%)	0.004*	2.07
iv	9 (47.4%)	19 (79.2%)		(1.56–19.4)
Total Mg Dose (g)				
≥ 24	14 (73.7%)	11 (45.8%)	0.027*	2.01
< 24	5 (26.3%)	13 (54.2%)		(1.51–1.75)
Length of administration (hour)				
≥ 24	14 (73.7%)	11 (45.8%)	0.027*	2.01
< 24	5 (26.3%)	13 (54.2%)		(1.51–1.75)

Apgar scores, lower birth weights, and a higher SGA and perinatal dea:h rate (Table 4). The perinatal death rate in the case group was 36.8% compared with 6.6% in the control group.

Discussion

The results of this study confirm that while the incidence of Mg intoxication in women with PESF treated with $MgSO_4$ is quite low (1,09%), Mg intoxication is associated with significantly increased adverse maternal and perinatal outcomes. The incidence of Mg intoxication in a large systematic review involving 9556 women, was 1.3–1.6% (8). Duley et al., in another large meta-analytic study, also found that Mg intoxicaton was rare and only occurred in around 1% of women receiving $MgSO_4$ (20). Importantly, Mg intoxication was not seen in patients receiving the "Magpie protocol' (5).

Three maternal deaths occurred among the 19 Mg intoxicated women, but the cause of maternal death was not directly related to the Mg level. The cause of death in these three cases was: septic shock, thyroid crisis, and intracerebral hemorrhage. Serum Mg level in these three cases had normalized a couple of days before they died. Lowe et al. reported no maternal death in their large systematic review, while Duley

Table 4. Perinatal outcomes of cases versus controls.

	Cases n = 19	Controls n = 166	*p* value	OR (95% CI)
Baby sex				
Male	13 (68.4%)	79 (50.3%)	0.131	NA
Female	6 (31.6%)	78 (49.7%)		
Baby Birthweight	1516.67 + 565.015	1872.32 + 662.860	0.005*	NA
Apgar Score				
Minutes 1	2.75 + 2.179	5.57 + 2.250	0.000*	NA
Minutes 5	5.42 + 1.782	7.34 + 1.573	0.000*	NA
SGA				
Yes	6 (31.6%)	14 (8.4%)	0.002*	3.74
No	13 (68.4%)	152 (91.6%)		(2.66–11.38)
Perinatal Death				
Yes	7 (36.8%)	11 (6.6%)	0.000*	5.56
No	12 (63.2%)	155 (93.4%)		(2.29–5.94)

et al. found two trials reported maternal deaths (8,20). The highest serum Mg level found among the cases in the current study was 25.6 mg/dL, this level is not considered to be high enough to directly cause maternal death. With serum levels of 20–34 mg/dL, Mg intoxication will be manifest as hypoventilation, acidosis, loss of tendon reflexes, and general weakness. Severe and life-threatening complications like respiratory depression and cardiac arrest will occur with the serum levels of 48–72 mg/dL (8). The clinical signs and symptoms in these Mg intoxication cases were general muscle weakness (loss of patellar reflex), loss of consciousness, and respiratory distress. The overall incidence of loss of patellar reflexes, loss of consciousness, and respiratory depression among all 1743 patients receiving $MgSO_4$ treatment was, respectively, 0.4% (8 cases), 0.5% (9 cases), and 0.1% (2 cases). The side effects caused by $MgSO_4$ treatment found in this study were significantly lower compared with the large systematic review by Lowe et al. (8). This review is comparable to our study since the research sample was only taken from middle- and low-income countries. The overall incidence of loss of patellar reflexes and respiratory distress in this systematic review was 1.2% and 1.3% (8). Unfortunately, this review did not evaluate the clinical sign of loss of consciousness. Perhaps this sign is not commonly interpreted as one of the major manifestations of Mg intoxication. The possible explanation of the much higher incidence of side effects reported in Lowe et al. (8) review compared with our study may be related to the regimen choices. Only eight studies used the Zuspan regimen (which is the same regimen used in our hospital) (18), while the other studies used the Pritchard (19) or the Dhaka regimens (21) with a relatively higher total dose of $MgSO_4$. Administration of $MgSO_4$ longer than 24 hours and a total dose of more than 24 grams would be potentially hazardous for the maternal outcome, as seen in the current study.

Interestingly, intramuscular administration of $MgSO_4$ was associated with a doubling of the rate of Mg intoxication; 52.6% of patients in the case group received $MgSO_4$ intramuscular versus 21.8% in the control group ($p = 0.004$). Similar findings have been reported by Kanti et al. (21); these authors reported a higher rate of signs and symptoms indicative of Mg intoxication and local site complications to be associated with intramuscular Mg administration. The Magpie trial also showed that intravenous administration had fewer side effects compared with the intramuscular route (5).

In the current study, the majority of the cases received intramuscular $MgSO_4$, since most of these patients were referred from primary health centers or primary health care or rural areas. This is in line with the regional referral guidelines on the management of PESF. Our regional policy for community-based care (primary health care) is to give a loading dose following the Pritchard regimen as initial management of PESF, before transferring the patients to a tertiary center. This approach has been implemented in many low- and middle-income countries such as Bangladesh, and India (22). The majority of smaller Indonesian medical centers prefer Pritchard IM administration regimen because of ease of administration, non-availability of infusion set/syringe pump, lack of nursing staff, and the fact that intramuscular administration is more cost-effective compared with iv regimen (23). Encouraging the government to provide syringe-pump availability throughout the nation could potentially improve outcomes in Indonesian women with PESF.

In our tertiary referral center, $MgSO_4$ is given via an intravenous route (syringe pump infusion) following the Zuspan regimen (18,22). Maintaining the therapeutic level of Mg while monitoring for sign of Mg

intoxication is important. Simple clinical assessment is adequate in most PESF women treated with $MgSO_4$, and more suitable in low- and middle-income countries (5,12,22), as is also demonstrated by the low overall rate of just over 1% in the current series.

The incidence of eclampsia and HELLP syndrome was significantly higher in the case group, while unexpectedly acute pulmonary edema, a common PE complication in Indonesia (15) was not seen among the 19 Mg intoxication cases. The presence of these complications may represent a significant risk factor of Mg intoxication due to the clinical necessity for a more prolonged $MgSO_4$ administration. Among the cases, more women received $MgSO_4$ for more than 5 days compared with the controls, although the average length of hospital stay between both groups did not differ significantly (cases versus controls: 10.21 ± 8.43 versus 11.29 ± 15.20, $p = 0.783$). The study results appear to indicate that giving $MgSO_4$ for more than 24 hours is not advisable unless Mg levels can be checked at regular intervals.

Another significant risk factor that could be contributing to the occurrence of Mg intoxication is oliguria and renal insufficiency. In this series, Mg-intoxicated patients had a worse renal function, reflected by higher BUN and serum creatinine level. Almost all of the serum magnesium is cleared by renal excretion, so any problems of urine production will significantly increase the risk of magnesium intoxication (6).

All patients in the Mg intoxicated group received calcium gluconate therapy as immediate management in line with our national protocol. This routine intervention is not found in the large systematic review by Lowe et al. The use of calcium gluconate in their review was extremely rare (0.18%). There is no clear explanation of this finding. However, Lowe et al. assumed that the low use of calcium gluconate reflects an infrequent need for its use as an antidote, rather than the unavailability of the drugs in the hospital (8,24).

The case had a higher rate of perinatal death, SGA, and low Apgar scores. Seven perinatal deaths (4 fetal demise) (36.8%) occurred in Mg-intoxicated group compared with 11 deaths (6.6%) in the control group. The higher rate of SGA in the case group reflects disease severity. About one-third of the cases were delivered of neonates who developed respiratory distress syndrome (RDS), significantly different from the 4% in the control group. Low Apgar scores were also more prominent among cases, in line with the strong correlation between maternal and fetal Mg levels resulting in respiratory muscle suppression and general muscle weakness. Previously, the use of antenatal $MgSO_4$ was discouraged by the majority of neonatologists because of a perceived risk of neonatal respiratory depression (25). However, recent studies with a large number of subjects have shown that particular concerns regarding the use of antenatal $MgSO_4$ for adverse neonatal implications were only encountered after long duration of Mg administration (26). We also discourage the prolonged use of antenatal $MgSO_4$ in PESF cases, not only because of the aforementioned neonatal concern but also because of the association with an increased risk of maternal and perinatal complications. The meta-analytic study by Duley et al. did not find any difference in the risk of stillbirth or neonatal death, but there was a small increase in the overall risk of perinatal mortality associated with $MgSO_4$ use (RR 1.04) (27).

Conclusion

Mg intoxication was found in just over 1% of PESF women treated with $MgSO_4$, as was found to be associated with a significant risk to the mother and fetus. While Mg serum levels cannot be measured as a routine in many developing countries, serial monitoring for the simple clinical signs and symptoms indicative of Mg intoxication is effective as a monitoring tool. In these countries, Mg serum level monitoring is indicated in patients requiring longer duration and higher accumulated doses of $MgSO_4$, both carry a high risk of Mg intoxication.

Acknowledgments

We thank Prof. Dr. Hendy Hendarto dr. SpOG(K) as the head of department who supported and gave permission to perform this study; we thank all staff in Department Obstetrics & Gynecology Faculty of Medicine Universitas Airlangga - RSUD Dr. Soetomo - RS Universitas Airlangga for their genuine support for this study; we thank our resident in training and the research team for their hard work in collecting data in this study; and we would like to thank all the patients who were involved in this study, without their participation the study could never be completed.

Disclosure statement

The authors declare no conflict of interest.

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preeclampsia in the intention-to-treat paradigm. However, maternal vitamin D levels ≥30 ng/mL at trial entry and in late pregnancy were associated with a lower risk of preeclampsia [60].

Discussion

The current review highlights the various management strategies in preeclampsia based in its pathological derangements; and these strategies are summarized in Table 1.

Despite all advances, the review demonstrates that preeclampsia is still difficult to 'defeat'. The clinician should differentiate between methods used to 'prevent' preeclampsia (in high risk patients) and methods used to 'treat' preeclampsia (meant to prolong the pregnancy in patients with preeclampsia). Table 2 shows these modalities and demonstrates that some of the medications are suitable for both prevention and treatment.

A) Preventive methods:

A classic example to demonstrate prevention is a patient with a history of preeclampsia and IUCD in place. The patient decides to remove the IUCD to conceive. All previous studies attempted to study the effect of a single method or drug to prevent the disease in such high risk patients and the results have been modest at best. The author of the current review recommends a protocol that combines multiple safe preventive methods in a multi-center trial.

It is well known that the risk of preeclampsia is higher in women with pre-existing obesity [61], dyslipidemia (particularly hypertriglyceridemia and hypercholesterolemia) [62], poorly controlled diabetes mellitus [63], obstructive sleep apnea (chronic hypoxemia) [64]. Hence, weight reduction, correction of the abnormal lipid profile, strict control of blood sugar and surgical treatment of sleep apnea should be implemented in high risk patients.

Adding a low molecular weight heparin to aspirin showed a modest beneficial preventive effect [36]; but it may prove more effective if combined with other preventive methods.

Recent studies [40,41] showed that L-arginine or isosorbid mononitrate (both enhance the production endothelial nitric oxide) will not only lower the incidence of preeclampsia, but will also improve intrauterine growth and fetal outcome. Hence, enhancement of nitric oxide production should be part of the preventive protocol.

Even in patients with no pre-existing dyslipidemia, statins should be included in the preventive protocol because of their known positive effects in inducing the HO pathway and in reducing the risk of preeclampsia [45].

Furthermore, metformin (as an inhibitor of HIF-1α) and curcumin (as an anti TLR4 receptor) proved effective and are worth including in preventive protocols [47,57].

Finally, the author believes that vitamin D should be included in the multi-agent preventive protocol as stressed by Mirzakhani et al. [60]. Vitamin D levels should be ≥30 ng/ml prior to and throughout pregnancy [60]. If the levels of vitamin D are low after conception, vitamin D replacement is not effective in preventing preeclampsia [60].

B) Treatment of established preeclampsia:

Treatment of preeclampsia is more difficult than its prevention. Our literature review showed that the pathology of an established preeclampsia cannot be completely reversed or arrested. Hence, current 'treatment' methods are meant to slow down the pathological process in order to prolong pregnancy. Besides the standard treatment methods of treating hypertension, aspirin and control of blood sugar and renal function; a multi-center treatment protocol is needed to include several new treatment modalities in the same protocol.

From the current review, the following medications have proven safe and effective in prolonging the pregnancy: Sildenafil as a vasodilator [32], esomeprazole as an inhibitor of vesicle shedding [46], metformin as an inhibitor of HIF-1α [47], hydroxy-chloroquine as an antagonist of TNF-α [54], and curcumin as an anti-TLR4 receptors [57]. It should be noted that all these medications have been tried individually in preeclampsia and showed their ability to prolong the pregnancy for 2–4 days only (enough for the steroid therapy for fetal lung maturity). However, the effectiveness of using multiple medications is unknown and may prove more effective in pregnancy prolongation.

More invasive treatment methods have also proven effective in pregnancy prolongation such as recombinant placental growth factor injections [51] and dextran sulfate apheresis to remove circulating sFlt-1 [48]. These more invasive methods may be indicated in early-onset/severe cases. The most impressive period of pregnancy prolongation in preeclampsia was a mean of 15 days with apheresis [48].

Table 1
Management strategies in preeclampsia based on its pathological derangements.

Pathology	Management strategies
1) Oxidative stress	Antioxidants (such as silymarin)
2) Formation of micro-emboli in the small vascular bed	Aspirin, low molecular weight heparin, antithrombin infusion
3) Vasoconstriction	Vasodilators (sildenafil citrate), Nitric oxide donors (glycerol trinitrate, isosorbid mononitrate), nitric oxide precursors (L-arginine)
4) Excessive production of placental sFlt-1 and endoglin	A. Induction of the heme-oxygenase pathway (statins) B. Inhibition of syncytiotrophoblast vesicle shedding (gelsolin, esomeprazole) C. Inhibition of HIF-1α (metformin) D. Removal of circulating sFlt-1 (dextran sulfate apheresis)
5) Deficiency of circulating VEGF/PLGF	Replacing PLGF or VGEF; but the latter has side effects
6) Systemic inflammatory response (excessive TNF-α, TLR4 receptors)	A) Anti-TNF-α: TNF-α antagonists, aspirin hydroxy-chloroquine, apolipoprotein. B) Anti-TLR4 receptors: Curcumin, Vitamin D

sFlt-1 = Soluble fms-like tyrosine kinase 1; HIF1α = hypoxic inducible factor-1α; VGEF = Vascular endothelial growth factor; PLGF = Placental growth factor; TNF-α = Tumor necrosis factor-α; TLR4 = Toll-like receptor 4.

Table 2
Preventive and treatments methods in preeclampsia.

Preventive methods	Treatment methods
Weight loss/correct abnormal lipid profile/strict control of blood sugar in diabetics/treat any pre-existing sleep apnea	Strict control of blood sugar in diabetics, Hydralazine
Aspirin	Aspirin
Low molecular weight heparin	Low molecular weight heparin
L-arginine/Isosorbid mononitrate	Sildenafil
Statins	Esomeprazole
Metformin	Hydroxy-chloroquine
Curcumin	Curcumin
Vitamin D	Recombinant placental growth factor Dextran sulfate apheresis

Conflicts of interest

There is no conflict of interest.

Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 593–598

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Preeclampsia: A review of the pathogenesis and possible management strategies based on its pathophysiological derangements

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ARTICLE INFO

Article history:
Accepted 21 July 2017

Keywords:
Preeclampsia
Pathogenesis
Management

ABSTRACT

This review is divided into three parts. The first part briefly describes the pathogenesis of preeclampsia. This is followed by reviewing previously reported management strategies of the disease based on its pathophysiological derangements. Finally, the author defines the safe and acceptable methods/medications that may be used to 'prevent' preeclampsia (in high risk patients) and those that may be used to 'treat' preeclampsia (meant to prolong the pregnancy in patients with established preeclampsia). The review concludes that multi-center trials are required to include multiple drugs in the same management protocol.

Introduction

Preeclampsia is a disorder of pregnancy characterized by hypertension and proteinuria of ≥300 mg/day. It is a serious disorder which may lead to maternal and fetal morbidity and mortality. The aim of this paper is to review the pathogenesis of preeclampsia and possible management strategies based on these pathophysiological derangements.

Methods

We carried out a literature review using electronic databases of PubMed [MEDLINE], and ScienceDirect; accessing published work on the pathogenesis of preeclampsia and management from 2000 to 2017. We aimed: to highlight possible management strategies based on the pathophysiological derangements of preeclampsia. We used the following search terms: "preeclampsia", "pathogenesis", and "management".

Results

Pathogenesis of preeclampsia

A) Placental ischemia and the increased levels of soluble fms-like tyrosine kinase 1(sFlt-1) and soluble endoglin (sEng):

In normal pregnancy, the cytotrophoblasts of the placenta invade the uterine wall and replace the highly resistant uterine spiral arteries and arterioles with a low-resistance vascular system. This remodeling is defective in preeclampsia (probably secondary to altered immunological response at the fetal maternal interphase) leading to placental ischemia [1]. This leads to excessive production of sFlt-1 [2]. sFlt-1 binds in the blood to both the vascular endothelial growth factor (VEGF) and the placental growth factor (PLGF). The status of high sFlt-1 and low VEGF/PLGF contributes to the development of hypertension [2,3].

Placental ischemia is also known to induce placental secretion of endoglin; increasing the levels of sEng in the maternal blood. sEng participates in the transforming growth factor Beta pathway. Once again, the status of high sEng contributes to the development of hypertension and proteinuria [4].

B) The generalized multi-system vasoconstrictive state, oxidative stress, micro-emboli, and endothelial cell dysfunction:

Endothelial nitric oxide synthase (e-NOS) induces the synthesis of nitric oxide (NO) which acts to vasodilate the arteriolar bed. In preeclampsia, there is deficiency of e-NOS leading to vasoconstriction of the placental bed, the renal vasculature and the vascular bed of other organs [5].

Placental ischemia in preeclampsia is also associated with diminished expression of the anti-oxidant heme oxygenase-2 (HO-2) [6]; and this contributes to the increased oxidative stress of ischemia and the formation of micro-emboli [7].

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http://dx.doi.org/10.1016/j.tjog.2017.08.004
1028-4559/

The multi-organ ischemia induces the production of hypoxia-inducible factor 1-alpha (HIF-1α); and this contributes to the abnormal placental function as well as the induction of elevated levels of sFlt-1 [8].

Preeclampsia is also associated with an increased sensitivity to the vasoconstrictive actions of angiotensin II; and this leads to renal dysfunction [9]. Endothelin 1 released from the placenta is another potent vasoconstrictor which is increased in preeclampsia [10]. Another reason for the vasoconstrictive state in preeclampsia is the imbalance between the vasoconstrictive thromboxane A2 and the vasodilator prostacyclin [11,12].

A controversial theory of pathogenesis is the genetic predisposition to preeclampsia secondary to apolipoprotein E (Apo E) polymorphism [13,14]. Certain Apo E alleles are associated with dyslipidemia which may contribute to endothelial cell dysfunction [14]. Furthermore, the Apo E-knockout homozygous mice model is a well-known animal model of preeclampsia featuring hypertension, proteinuria and increased expression of sFlt-1 [15].

C) The systemic inflammatory response:

Toll-like receptor 4 (TLR4 receptors) are most abundant in the placenta, leukocytes, and renal podocytes. These receptors are responsible for the induction of inflammatory cytokines. Preeclampsia is associated with over-expression of placental and renal TLR4 leading to an increase in inflammatory cytokines and placental/renal dysfunction [15,16]. Furthermore, very high levels of TLR4 receptors are associated with early onset preeclampsia and HELP (Hemolysis, Elevated Liver enzyme, and low Platelets) syndrome of preeclampsia [17].

In cytomegalovirus (CMV)-seropositive mothers, the monocyte is the major cell type harboring the virus in a latent state. These mothers are at high risk of CMV reactivation during pregnancy and this contributes to the over-expression of TLR4 [17].

The risk of eclampsia is higher in mothers with low level of Vitamin D. Vitamin D deficiency is known to induce pro-inflammatory cytokines and the over expression of TLR4 receptors; participating in the pathogenesis of preeclampsia [18,19].

Preeclampsia is not only associated with an increase in pro-inflammatory cytokines, but is also associated with a decrease in anti-inflammatory cytokines [20,21]. The most important pro-inflammatory cytokines are interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), and the pro-inflammatory interleukins (IL): IL-1, -2, -6, -8, -15, -16, and -18 [22]. In fact, preeclamptic patients may have a genetic polymorphism of TNF-α and IL-1 resulting in increased levels of these cytokines [23]. Furthermore, acute phase reactants (such as the C-reactive protein) are higher in preeclampsia compared to normal pregnancy [20]. Finally, preeclampsia is associated with higher levels of serum heat shock protein 70 (Hsp 70) and the degree of elevation of Hsp 70 correlates with the degree of elevation of circulating pro-inflammatory cytokines in preeclampsia [24]. The end result is a state of systemic inflammatory response reaction leading to edema and extravasation; compounding the insults to the placental, renal, and other organ vascular beds.

D) Structural changes of the glycocalyx and hyaluronic acid leading to feto-maternal interface dysfunction:

Glycocalyx is expressed in the feto-maternal interface and mediate interactions between fetal and maternal cells. Placentas of women with preeclampsia show alterations of glycocalyx composition coating the endothelium and is thought to play an important role in the pathogenesis of intra-uterine growth retardation [25]. The reason for these alterations in composition of glycocalyx is unknown but they may be related to the systemic inflammatory response of preeclampsia [26].

Hyaluronic acid (HA) is a main component of the extracellular matrix. Normally, high molecular weight HA is predominant. In preeclampsia, there is predominance of low molecular weight HA. This alteration is also thought to participate in placental endothelial cell dysfunction of preeclampsia [26].

Syndecan-1 (Sdc1, also known as CD138) is a component of glycocalyx [27]. In preeclampsia, both the soluble and placental sdc1 are significantly lower when compared to controls [27].

Heparan sulfate is also a component of the glycocalyx; and it is interesting to note that the 3-0 sulfating enzyme of heparan sulfate is decreased in the placenta of preeclamptic women [28].

Management of preeclampsia in the current practice

Although preeclampsia is defined as hypertension with proteinuria, clinicians are aware that preeclampsia is a systemic disease. The blood flow to every maternal organ is reduced with vasoconstriction and microthrombi formation ending in multi-organ dysfunction. Simultaneously, fetal complications and growth retardation occur secondary to placental hypo-perfusion. The current management strategies of preeclampsia is based on the diagnosis of the disease, the assessment of its severity, anti-hypertensive therapy, and finally deciding on the timing of delivery. Intrapartum treatment includes seizure prophylaxis (usually by magnesium sulfate), control of blood pressure (usually by hydralazine) and appropriate intravenous fluid management [29,30]. In other words, preeclampsia has defeated clinicians; forcing them to deliver these mothers to abort further fetal and maternal complications.

New management strategies in the current review are directed to reverse or arrest the pathological processes of preeclampsia or to prevent its occurrence in high risk patients; and hence defeating the disease.

Management strategies based on the pathological derangements in preeclampsia

Patients at high risk for preeclampsia should attend high-risk antenatal clinics and are usually given daily aspirin [31]. However, there is no clear evidence that these measures are effective in the prevention of preeclampsia. Dietary measures (such as chocolate and fish oil) have also been tired and proved ineffective in the prevention of the disease [32,33].

A. Management directed against the oxidative stress

Oxidative factors are involved in the pathogenesis of preeclampsia and the thrombocytopenia [34]. In a double-blind clinical trial, silymarin (a drug which has an antioxidant effect) did not have a positive effect in improving the abnormal parameters in patients with preeclampsia [34].

B. Management directed against the formation of micro-emboli

Several studies studied the effect of adding low-molecular-weight heparins to aspirin on the prevention of preeclampsia and demonstrated no positive effect [31,35]. However, a recent systematic review and meta-analysis found a modest beneficial effect and recommended further studies on the topic [36].

In patients with severe preeclampsia, antithrombin infusions may have a potential maternal benefit, but a recent trial did not support its use in patients with early/severe preeclampsia [37].

C. Management directed against the vasoconstrictive state in preeclampsia

Vasodilators have been tried clinically both to prolong pregnancy in women with preeclampsia and to prevent preeclampsia in patients with high risk factors for preeclampsia. Trapani et al. [38] conducted a randomized controlled trial to evaluate therapy with the vasodilator sildenafil citrate in preeclamptic women. Compared to controls (receiving a placebo), therapy with sildenafil was associated with pregnancy prolongation of 4 days.

The vasoconstrictive state of preeclampsia is associated with deficiency of endothelial nitric oxide with is a vasodilator to the arteriolar system [39]. Hence, the use of nitric oxide donors (such as glycerol trinitrate and isosorbid mononitrate) or nitric oxide precursors (such as L-arginine) is thought to be an attractive option for preventing preeclampsia in high risk patients. The Cochrane database systematic review of 2007 [39] could not find good quality trials to draw reliable conclusions on the effectiveness of nitric oxide donors/precursors to prevent preeclampsia. However, more recent studies clearly demonstrated that both nitric oxide donors (isosorbid mononitrate) and precursors (L-arginine) are effective in the prevention of preeclampsia [40,41]. Not only there was significantly lower incidence of preeclampsia in the treatment groups, but there was also a significant reduction in intrauterine growth restriction and neonatal admissions to the intensive care unit [40,41].

D. Management directed against the excessive production of sFlt-1 and sEng:

As mentioned earlier in the pathogenesis, the increased levels of sFlt-1 and sEng are the most prominent feature of preeclampsia. sFlt-1 is normally produced in the syncytiotrophoblast extracellular vesicles and is then released into the maternal blood. This process is greatly accelerated in preeclampsia [42]. Hence, the reduction of sFlt-1/sEng is an attractive method for the prevention and treatment of preeclampsia. This area has been extensively studied in the literature. In experimental preeclampsia mice models, the drug GYY4137 was effective in decreasing circulating sFlt-1 and sEng [43].

The author of the current review has classified methods used clinically to reduce the level of sFlt-1/sEng into four categories: Induction of the heme-oxygenase (HO) pathway, inhibition of syncytiotrophoblast extracellular vesicle shedding and secretion of sFlt-1/sEng, inhibition of hypoxic inducible factor 1α (HIF-1α) and removal of circulating sFlt-1 by dextran sulfate apheresis.

The HO pathway is known to inhibit sFlt-1/sEng [44]. Statins (drugs commonly used to lower cholesterol levels) induce the HO and hence suppress sFlt-1 and sEng [44]. In a recent review of the literature, Marrs and Costantine [45] stated that there is enough encouraging data from preclinical and pilot clinical studies to recommend statins (such as pravastatin) in clinical practice of preeclampsia and recommended the conduction of randomized controlled trials.

sFlt-1 is secreted into the maternal circulation from shedding of the syncytiotrophoblast extracellular vesicles. Recombinant human gelsolin supplementation has been shown to inhibit this shedding process; and hence reducing the levels of sFlt-1 [42]. Another drug (esomeprazole) was found to be a potent inhibitor of the secretion of both sFlt-1 and sEng from the placenta. Cluver et al. [46] announced the start of the PIE trial which is a double blind, randomized placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset preeclampsia.

sFlt-1 is excessively produced from the placenta secondary to hypoxia. There is sufficient evidence that HIF-1α (which is induced by hypoxia) is a main factor leading to the excessive production of sFlt-1 [47]. Hence, small molecule inhibitors of HIF-1α are known to reduce sFlt-1. However, the safety of these small molecules in pregnancy is unknown [47]. Metformin is safe in pregnancy and is a potent inhibitor of HIF-1α and has excellent potential to prevent and treat preeclampsia [47].

Finally, removal of circulating sFlt-1 is possible by dextran sulfate apheresis. Thadhani et al. [48] conducted an open pilot study to evaluate the efficacy of dextran sulfate apheresis in 11 women with early-onset preeclampsia. Compared to controls, treated women had reduced circulating sFIT-1 and reduced proteinuria. Furthermore, treated women had prolongation of their pregnancies by an average of 15 days (range 11–21 days) compared to controls.

E. Management directed to replace the deficiency of circulating VEGF and PLGF.

As mentioned in the pathogenesis, the elevated sFlt-1 binds in the circulation to both VEGF and LPGF resulting in endothelial dysfunction of the placenta and the systemic maternal vasculature. Several experimental studies in animal models of preeclampsia have shown the efficacy of intravenous VEGF and PLGF in reducing the elevated blood pressure and proteinuria [49,50]. Clinically, the use of VEGF causes edema because of its high affinity to VEGF-receptor 2 [51]. However, PLGF is specific for sFlt-1 and does not have adverse effects on the mother or fetus [51]. Hence recombinant human PLGF has a strong therapeutic potential in preeclampsia [51].

F. Management directed against the increased systemic inflammatory response in preeclampsia.

As mentioned earlier, the increased systemic inflammatory response plays a major role in the pathogenesis of preeclampsia. This inflammatory response is manifested by increased levels of pro-inflammatory cytokines (such as TNF-α), over expression of TLR4 receptors, elevated heat shock proteins, and the structural changes of placental glycocalyx (these structural changes are thought to be induced by the inflammatory response).

TNF-α antagonists are relatively safe in pregnancy and have potential to treat severe cases of preeclampsia [52]. Aspirin prevents TNF-α induced endothelial dysfunction [53]. Hydroxy-chloroquine (an anti-malarial drug) not only reduces the production of TNF-α, but it also reduces the levels of endothelin-1 in preeclampsia experimentally [54]. Hence, the use of hydroxychloroquine as an adjuvant therapy in preeclampsia requires an investigation in the clinical setting. Experimentally, the administration of apolipoprotein (a constituent of high density lipids and also acts as an anti-inflammatory agent) protects against the effects of TNF-α in human in-vitro models of trophoblast invasion in preeclampsia [55].

Another way to reduce the systemic inflammatory response of preeclampsia is to suppress or alter the TLR-4 receptor overexpression. Curcumin is extracted from plants and is commonly used as a herbal supplement and a food coloring additive. Chemically, curcumin is a phenol [56]. Curcumin is known to inhibit the TLR-4 signaling pathway [57]. In a rat preeclampsia model, Gong et al. showed the efficacy of curcumin in reducing placental TLR4 expression, reducing the blood pressure and normalizing the urinary protein levels in treated animals compared to the controls [57].

Another inhibitor of TLR4 is vitamin D [19]. Hence, vitamin D supplements are associated with significant reduction of proinflammatory cytokines [22,58]. High-dose supplementation (up to 35,000 IU/week) is relatively safe in pregnancy [59]. The trial of Mirzakhani et al. showed several important findings on the topic [60]. High dose vitamin D supplementation (4400 IU/day) initiated in weeks 10–18 of pregnancy did not reduce the incidence of

Acknowledgment

The work was supported by the College of Medicine Research Center, Deanship of Scientific Research King Saud University, Saudi Arabia.

References

[1] Hariharan N, Shoemker A, Wagner S. Pathophysiology of hypertension in preeclampsia. Clin Pract 2016;13:33–7.
[2] Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt-1) may contribute to endothelial dysfunction, hypertension and proteinuria in pregnancy. J Clin Investig 2003;111(5):649–58.
[3] Chaiworapongsa T, Romero R, Espinoza J, Bujold E, Mee Kim Y, Gonçalves LF, et al. Evidence supporting the role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Am J Obstet Gynecol 2004;190(6):1541–7.
[4] Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med 2006;12(6):642–9.
[5] Li F, Hagaman JR, Kim H, Maeda N, et al. eNOS deficiency acts through endothelia to aggravate sFlt-1 induced preeclamptic-like phenotype. J Am Soc Nephrol 2012;23(4):652–60.
[6] Zenclussen AC, Lim E, Knoeller S, Knackstedt M, Hertwig K, Hagen E, et al. Heme-oxygenase in pregnancy II: HO-2 is down regulated in human pathologic pregnancies. Am J Reprod Immunol 2003;50(1):66–76.
[7] Lyall F, Barber A, Myatt L, Bulmer JN, Robson SC. Heme-oxygenase expression in human placenta and placental bed implies a role in regulation of trophoblast invasion and placental function. FASEB J 2000;14(1):208–19.
[8] Iriyama T, Wang W, Parchim NF, Song A, Blackwell SC, Sibai BM, et al. Hypoxia-independent up regulation of placental hypoxia inducible factor 1 alpha gene expression contributes to the pathogenesis of preeclampsia. Hypertension 2015;65(6):1307–15.
[9] Zhou CC, Zhang Y, Irani RA, Zhang H, Mi T, Popek EJ, et al. Angiotensin receptor agonistic auto antibodies induce preeclampsia in pregnant mice. Nat Med 2008;14(8):855–62.
[10] Dekker GA, Kraayenbriak AA, Aeeman GG, Van Kamp GJ. Increased plasma levels of the novel vasoconstrictor peptide endothelia in severe preeclampsia. Eur J Obstet Gynecol Reprod Biol 1991;40:215–20.
[11] Wang Y, Walsh SW, Guo J, Zhang J. The imbalance between thromboxane and prostacyclin in preeclampsia is associated with an imbalance between lipid peroxidases and vitamin E in maternal blood. Am J Obstet Gynecol 1991;165(6):1695–700.
[12] Rocca B, Loeb AL, Strauss 3rd JF, Vezza R, Habib A, Li H, et al. Directed vascular expression of the thromboxane A2 receptor results in intrauterine growth retardation. Nat Med 2000;6(2):219–21.
[13] Francoual J, Audibert F, Trinche P, Chalas J, Capel L, Lindenbaum A, et al. Is a polymorphism of the apolipoprotein e-gene associated with preeclampsia? Hypertens Pregnancy 2002;21:127–33.
[14] Belo L, Gaffney D, Caslake M, Santos-Silva A, Pereira-Leite L, Quintanilha A, et al. Apolipoprotein E and cholesteryl ester transfer protein polymorphism in normal and preeclamptic pregnancies. Eur J Obstet Gynecol Reprod Biol 2004;112:9–15.
[15] Sun W, Cui B, Hong F, Xu Y. Establishment of Apo E-knockout mouse model of preeclampsia and relevant mechanisms. Exp Ther Med 2016;12:2634–8.
[16] Kulikova GV, Nizyaeva NV, Nagovitsina MN, Lyapin VM, Loginova NS, Kan NE, et al. Specific features of TLR4 expression in structural elements of placenta in patients with preeclampsia. Placenta 2016;43:69–76.
[17] Xie F, Van Dadelszen P, Nadeau J. CMV infection, TLR2 and -4 expression, and cytokine profiles in early-onset preeclampsia with HELLP syndrome. Am J Reprod Immunol 2014;71(4):379–86.
[18] Halhali A, Díaz L, Barrera D, Ávila E, Larrea F. Placental calcitriol synthesis and IGF-1 levels in normal and preeclamptic pregnancies. Clin Chir Acta 2011;412(21–22):1957–62.
[19] Qian L, Wang H, Wu F, Li M, Chen W, Lianzeng LV. Vitamin D3 alters TOLL-like receptor 4 signaling in monocytes of pregnant women at risk of preeclampsia. Int J Cin Exp Med 2015;8(10):18043–9.
[20] Mihn D, Razvun C, Malutun A, Michaela C. Evaluation of maternal systemic inflammatory response in preeclampsia. Taiwan J Obstet Gynecol 2015;54:100–6.
[21] Denney JM, Nelson EL, Wadhwa PD, Waters TP, Mathew L, Chung EK, et al. Longitudinal modulation of immune system cytokine profile during pregnancy. Cytokine 2011;53:170–7.
[22] Barrera D, Díaz L, Noyola-Martínez N, Halhali A. Vitamin D and inflammatory cytokines in healthy and preeclamptic pregnancies. Nutrients 2015;7:6465–90.
[23] Haggerty CL, Ferrell RE, Hubel CA, Markovic N, Harger G, Ness RB. Association between allelic variants in cytokine genes and preeclampsia. Am J Obstet Gynecol 2005;193:209–15.
[24] Molvarec A, Szarka A, Walentin S, Beko G, Karádi I, Prohaszka Z, et al. Serum heat shock protein 70 levels in relation to circulating cytokines, chemokines, adhesion molecules and angiogenic factors in women with preeclampsia. Clin Chim Acta 2011;412(21–22):1957–62.
[25] Sukhikh GT, Ziganshina MM, Nizyaeva NV, Kulikova GV, Volkova JS, Yarotskaya EL, et al. Differences of glycocalyx composition as the structural elements of placenta in preeclampsia. Placenta 2016;43:89–76.
[26] Ziganshina MM, Pavlovich SV, Bovin NV, Sukhikh GT. Hyaluronic acid in vascular and immune homeostasis during normal pregnancy and preeclampsia. Acta Naturae 2016;8:59–71.
[27] Gandley RE, Althouse A, Jeyabalan A, Bregand-White JM, McGonigal S, Myerski AC, et al. Low soluble syndecan-1 precedes preeclampsia. PLoS One 2016;11(6):e0157608.
[28] Amraoui F, Hassani-Lahsinoui H, Bonssata S, Keijser R, Veenboer GJ, Middeldorp S, et al. Placental expression of heparin sulfate 30-sulotransferase -3A7 in normotensive and preeclamptic pregnancies. Placenta 2015;36:1218–24.
[29] Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA 2002;287:3183–6.
[30] Euser AG, Cipolla MJ. Magnesium sulfate treatment for the prevention of eclampsia: a brief review. Stroke 2009;40:1169–75.
[31] Groom KM, McCowan LM, Mackay LK, Lee AC, Said JM, Kane SC, et al. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: a randomized trial. Am J Obstet Gynecol 2017. http://dx.doi.org/10.1016/j.ajog.2017.01.014.
[32] Bujold E, Leblanc V, Lavoie-Lebel E, Babar A, Girard M, Pougnui L, et al. High-flavanol and high-theobromine versus low flavanol and low-theobromine chocolate to improve uterine artery pulsatility index: a double blind randomized clinical trial. J Matern Fetal Neonatal Med 2016. http://dx.doi.org/10.1080/14767058.2016.1236250.
[33] Chen B, Ji X, Zhany L, Hou Z, Li C, Tong Y. Fish oil supplementation does not reduce risks of gestational diabetes mellitus, pregnancy-induced hypertension, or preeclampsia: a meta-analysis of randomized controlled trials. Med Sci Monit 21:2322–2330. doi:10.12659/MSM.894033.
[34] Raghibabadocani FK, Miraj S. The impact of silymarin on improvement of platelet abnormalities in patients with severe preeclampsia. Electron Physician 2016;8:2436–42.
[35] Van Hoorn ME, Haque WM, Van Pampus ME, Bezener D, de Vries JI. Low molecular weight heparin and aspirin in the prevention of recurrent early onset preeclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. Eur J Obstet Gynecol Reprod Biol 2016;197:168–73.
[36] Mastrolia SA, Novack L, Thachil J, Rabinovich A, Pikovsky O, Klaitman V, et al. LMWH in the prevention of preeclampsia and fetal growth restriction in women without thrombophilia. A systematic review and meta-analysis. Thromb Haemost 2016;116:868–78.
[37] D'Angle A, Valsecchi L. At III-early preeclampsia study group, high dose antithrombin supplementation in early preeclampsia: a randomized double-blind placebo controlled study. Thromb Res 2016;140:7–13.
[38] Trapani Jr A, Goncalves LF, Trapani TF, Vieira S, Pires M, Pires MM. Perinatal and hemodynamic evaluation of Sildenafil citrate for preeclampsia treatment: a randomized controlled trial. Obstet Gynecol 2016;128:253–9.
[39] Meher S, Duley L. Nitric oxide for preventing preeclampsia and its complications. Cochrane Database Syst Rev 2007;2. CD006490.
[40] Camarena Pulido EE, García Benavides L, Panduro Barón JG, Pascoe Gonzalez S, Madrigal Saray AJ, García Padilla FE, et al. Efficacy of L-arginine for preventing preeclampsia in high risk pregnancies: a double-blind randomized clinical trial. Hypertens Pregnancy 2016;35:217–25.
[41] Abdelrazik M, ElBerry S, Aboserea M, Edris Y, Sharafeldeen A. Prophylactic treatment for preeclampsia in high risk teenage primigravida with nitric oxide donors: a pilot study. J Matern Fetal Neonatal Med 2016;29:2617–20.
[42] Nadkarni NA, Rajakumar A, Mokhashi N, Burke SD, Rana S, Salahuddin S, et al. Gelsolin is an endogenous inhibitor of syncytiotrophoblast extracellular vesicle shedding in pregnancy. Pregnancy Hypertens 2016;6:333–9.
[43] Ahmed A. Molecular mechanisms and therapeutic implications of the carbon monoxide/hmox1 and the hydrogen sulfide/CSE pathways in the prevention of preeclampsia and fetal growth restriction. Pregnancy Hypertens 2014;4:243–4.
[44] Ramma W, Ahmed A. Therapeutic potential of statins and the induction of heme oxygenase-1 in preeclampsia. J Reprod Immunol 2014;101–102:153–60.
[45] Marrs CC, Costantine MM. Should we add pravastatin to aspirin for preeclampsia prevention in high risk women? Clin Obstet Gynecol 2017;00:101–8.
[46] Cluver CA, Walker SP, Mol BW, Theron GB, Hall DR, Hiscock R, et al. Double-blind, randomized, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset preeclampsia (PVE trial): a study protocol. BMJ Open 2015;5:e008211. http://dx.doi.org/10.1136/bmjopen.
[47] Brownfoot FC, Hastie R, Hannan NJ, Cannon P, Tuohey L, Parry LJ, et al. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. Am J Obstet Gynecol 2016;214:356. http://dx.doi.org/10.1016/j.ajog.2015.12.019. E1-356.e15.
[48] Thadhani R, Hagmann H, Schaarschmidt W, Roth B, Cingoez T, Karumanchi SA, et al. Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. J Am Soc Nephrol 2016;27:903–13.
[49] Suzuki H, Ohkuchi A, Matsubara S, Takei Y, Murakami M, Shibuya M, et al. Effect of recombinant placental growth factor 2 on hypertension induced by full-length mouse soluble fms-like tyrosine kinase 1 adenoviral vector in pregnant mice. Hypertension 2009;54:1129–35.

[50] Makris A, Yeung KR, Lim SM, Sunderland N, Heffernan S, Thompson JF, et al. Placental growth factor reduces blood pressure in a utero placental ischemia model of preeclampsia in non- human primates. Hypertension 2016;67:1263–72.
[51] Spradley FT, Tan AY, Joo WS, Daniels G, Kussie P, Karumanchi SA, et al. Placental growth factor administration abolishes placental ischemia-induced hypertension. Hypertension 2016;67:740–7.
[52] Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, Llurba E, Gris JM. Tumor necrosis factor-alpha and pregnancy: focus on biologics. An updated and comprehensive review. Clin Rev Allergy Immunol 2017. http://dx.doi.org/10.1007/s12016-016-8596-x.
[53] Kim J, Lee KS, Kim JH, Lee DK, Park M, Choi S, et al. Aspirin prevents TNF-α induced endothelial cell dysfunction by regulating the NF-κB dependent miR-155/eNOS pathway: role of a miR-155eNOS axis in preeclampsia. Free Radic Biol Med 2017;104:185–98.
[54] Rahman R, Murthi P, Singh H, Gurusinghe S, Mockler JC, Lim R, et al. The effects of hydroxychloroquine an endothelial dysfunction. Pregnancy Hypertens 2016;6:259–62.
[55] Charlton F, Bobek G, Stait-Gardner T, Price WS, Mirabito Colafella KM, Xu B, et al. The protection effect of apolipoprotein in models of trophoblast invasion and preeclampsia. Am J Physiol Regul Integr Comp Physiol 2017;312:840–8.
[56] Hsu CH, Cheng AL. Clinical studies with curcumin. Adv Exp Med Biol 2007;595:471–80.
[57] Gong P, Liu M, Hong G, Li Y, Xue P, Zheng M, et al. Curcumin improves LPS-induced preeclampsia-like phenotype in rat by inhibiting the TLR4 signaling pathway. Placenta 2016;41:43–52.
[58] Seng J, Li Y, An R. Vitamin D restores angiogenic balance and decrease tumor necrosis factor in a rat model of preeclampsia. J Obstet Gynaecol Res 2017;43:42–9.
[59] Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, et al. Randomized placebo-controlled trial of high dose prenatal third trimester Vit D3 supplementation in Bangladesh: the AV: DD trial. Nutr J 2013;12:47. http://dx.doi.org/10.1186/1475-2891-12-47.
[60] Mirzakhani H, Litonjua AA, McElrath TF, O'Connor G, Lee-Parritz A, Iverson R, et al. Early pregnancy vitamin D status and risk of preeclampsia. J Clin Investig 2016;126:4702–15.
[61] Spradley FT. Metabolic abnormalities and obesity's impact on the risk for developing preeclampsia. Am J Physiol Regul Integr Comp Physiol 2017;312:R5–12.
[62] ElKhouley NI, Sanad ZF, Saleh SA, Shabana AA, Elhalaby AF, Badr EE. Value of first trimester serum lipid profile in early prediction of preeclampsia and its severity: a prospective cohort study. Hypertens Pregnancy 2016;35:73–81.
[63] Jong HJ, Kim HS, Kim SH. Maternal and neonatal outcomes in Korean women with type 2 diabetes. Korean J Intern Med 2017. http://dx.doi.org/10.3904/kjim.2016.105.
[64] Facco FL, Parker CB, Reddy UM, Silver RM, Koch MA, Louis JM, et al. Association between sleep-disordered breathing and hypertension disorders of pregnancy and gestational diabetes mellitus. Obstet Gynecol 2017;129:31–41.

International Journal of Women's Health

Dovepress

REVIEW

Retained placenta after vaginal delivery: risk factors and management

This article was published in the following Dove Press journal:
International Journal of Women's Health

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Abstract: Retained placenta after vaginal delivery is diagnosed when a placenta does not spontaneously deliver within a designated amount of time, variably defined as a period of 18–60 mins. It may also be diagnosed if a patient experiences significant hemorrhage prior to delivery of the placenta. Normal placenta delivery requires adequate uterine contractions, with shearing of the placenta and decidua from the uterine wall and expulsion of the tissue. Thus, retained placenta can occur in the setting of significant uterine atony, abnormally adherent placenta, as with placenta accreta spectrum (PAS), or closure of the cervix prior to placental expulsion. Risk factors for retained placenta parallel those for uterine atony and PAS and include prolonged oxytocin use, high parity, preterm delivery, history of uterine surgery, and IVF conceptions. History of a prior retained placenta and congenital uterine anomalies also appear to be risk factors. Management entails manual removal of the placenta with adequate analgesia, as medical intervention alone has not been proven effective. Complications can include major hemorrhage, endometritis, or retained portions of placental tissue, the latter of which can lead to delayed hemorrhage or infection. Prophylactic antibiotics can be considered with manual placenta removal, though evidence regarding effectiveness is inconsistent. If hemorrhage is encountered, deployment of a massive transfusion protocol, uterine evacuation with suction, and use of intrauterine tamponade, as with an intrauterine balloon, should be initiated immediately. When a separation plane between the placenta and uterus is particularly difficult to create, PAS should be considered, and preparations should be made for hemorrhage and hysterectomy. Patients with risk factors for retained placenta should have a laboratory sample sent for blood type and antibody screening on admission to labor and delivery, and plans should be made for appropriate analgesia and preparations for hemorrhage if a retained placenta is encountered.

Keywords: retained placenta, manual removal of the placenta, postpartum hemorrhage, placenta accreta spectrum

Introduction

Retained placenta after vaginal delivery, which occurs in around 1–3% of deliveries, is a relatively common cause of obstetrical morbidity. This is typically diagnosed when the placenta fails to spontaneously separate during the third stage of labor when a patient experiences excessive bleeding in absence of placenta separation or if there is confirmation of placenta tissue remaining after the majority of the placenta delivers spontaneously.[1–3] Placentas that fail to spontaneously separate can be a cause of significant surgical and hemorrhagic morbidity.[4,5] Untreated, retained placenta is considered the second leading cause of postpartum hemorrhage (PPH).[5,6]

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Although retained placenta is an obstetrical complication encountered relatively infrequently on the labor and delivery floor, recognizing patient risk factors and understanding management are important steps in mitigating this morbidity.

Pathophysiology

Normal placentation begins with blastocyst implantation into the maternal endometrium. In preparation for this implantation, the endometrium develops the decidua under the influence of progesterone and estrogen in early pregnancy. As the blastocyst invades this decidua, the layer of cells forming the surface of the blastocyst develops into the chorionic membrane. Cytotrophoblast cells proliferate from the chorionic membrane and form multinucleated aggregates called syncytiotrophoblast cells. These cells form the placental villi, allowing fetal–maternal interchange between the villi–decidual interaction. With delivery of the infant, both a hormonal cascade and uterine contractions allow for separation of these layers and expulsion of the placenta.[7]

Retained placenta is generally attributed to one of three pathophysiologies. First, an atonic uterus with poor contraction may prevent normal separation and contractile expulsion of the placenta.[2,8,9] Second, an abnormally adherent or invasive placenta, as seen with placenta accreta spectrum (PAS), may be incapable of normal separation. Finally, a separated placenta may be trapped or incarcerated due to closure of the cervix prior to delivery of the placenta.[2,8–10] Placental hypoperfusion disorders, such as with preeclampsia, and infection have also been proposed as mechanisms for retained placenta, although little is known about the specific mechanism.[9,11]

Epidemiology

Estimates of retained placenta put the incidence at between 0.1% and 3%.[5,8] Prospective investigations of retained placenta confirm these estimates, with one study of >45,000 patients showing that overall for all gestational ages, retained placenta happened in about 3% of deliveries, with gestational ages of <26 weeks and <37 weeks having a significantly increased risk of retained placenta requiring manual removal.[1] Generally, incidence seems to be higher in developed countries where practices tend toward earlier manual removal of the placenta in the third stage of labor.[8,12]

Risk factors

Many studies have attempted to define risk factors for retained placenta, which are listed in Table 1. Established risk factors include prior retained placenta, preterm delivery, prior uterine surgery, previous pregnancy termination, miscarriage or curettage, grand multiparity (greater than five prior deliveries), and congenital uterine anomalies (often unrecognized prior to delivery).[3,5,11]

Table 1 Risk factors for retained placenta

Risk factors related to poor uterine contraction
High parity Prolonged use of oxytocin
Risk factors related to abnormal placentation
History of uterine surgery IVF conception
Other risk factors
Preterm delivery Congenital uterine anomaly Prior history of retained placenta

Some studies have suggested that prolonged oxytocin use could be a potentially modifiable risk factor for retained placenta, with one study reporting that oxytocin use for over 195 mins increased the odds ratio of the retained placenta by 2.0, and oxytocin use over 415 mins increased the odds ratio by 6.5.[5] It is less clear whether oxytocin is directly involved in placental retention, or if the association is mediated by uterine atony or infection due to prolonged labor.

Placental under perfusion disorders have been implicated as risk factors for retained placenta.[11] In a case–control study of all singleton primiparous vaginal deliveries in Sweden between 1997 and 2009, the authors found an increased association between placental under perfusion disorders (such as preeclampsia, small for gestational age, and stillbirth) and retained placenta; however, they could not designate a common pathophysiology.

Some research suggests that women may be predisposed to retained placenta. Retained placenta in a prior delivery appears to be an important risk factor for recurrence. In one study of over 280 women in Denmark, prevalence of retained placenta was found to be consistent with previously reported numbers (approximately 3%) using strict diagnostic criteria. The authors found that in subsequent vaginal deliveries, the risk of recurrence was substantially increased to about 25%.[3] There has even been some suggestion that tendency toward retained placenta may even be inherited. In one study, authors used the Swedish Medical Birth Register to identify women with

retained placenta after 1992 whose mothers' own birth records were also in the Register (after 1973). The authors found that the risk of retained placenta increased if retained placenta had occurred at the mother's own birth (aOR 1.66 95% CI 1/52–1/82), at the birth of one of her siblings (aOR 1.58, 95% CI 1.43–1.76), or both (aOR 2.75, 95% CI 2.18–3.46).[13]

Because of its relationship to PAS, assisted reproductive technologies (IVF or ICSI) have been proposed and studied as an additional risk factor for retained placenta.[14] Elenis et al, in a 2015 study from Sweden, looked specifically at oocyte donation IVF and the risk of poor obstetrical outcomes in otherwise healthy women.[15] The authors found a positive association between retained placenta and oocyte donation, as well as between PPH and oocyte donation.[15] In another 2016 study by Aziz et al, seeking to determine whether or not length of third stage was related to IVF, the authors concluded that cryopreserved embryo transfer (donated or autologous) without controlled ovarian hyperstimulation was not related to longer third stage, but did significantly increase the risk for manual removal of the placenta.[16]

Morbidity

Retained placenta requiring invasive procedures is associated with obstetrical morbidities. Of arguably greatest significance is the risk of postpartum hemorrhage, with retained placenta the second leading cause of significant and even fatal hemorrhage in the obstetric population.[5,17] One group found that the odds ratio related to estimated blood loss exceeding 500 mL, 1000 mL, and 2000 mL with retained placenta, respectively, is as high as 33.07 (95% CI 20.57–53.16), 43.44 (95% CI 26.57–71.02), and 111.24 (95% CI 27.26–454.00).[5] In another case–control study of 114 women with manual removal for retained placenta, the authors found that the case group required significantly more blood transfusions (13% in the case group versus 0% in the controls).[18] Large cohort studies have confirmed this elevated risk.[17]

Further research additionally suggests that the longer the third stage of labor, the greater the risk of postpartum hemorrhage.[19] A study by Dombrowski et al in 1995 tried to determine gestational age–specific data for the length of the third stage, retained placenta, hemorrhage, and manual removal. The authors found that both manual removal of the placenta and PPH decreased with increasing gestational age, and that the two were related. However, causal association could not be determined.[1]

If the placenta or pieces of the placenta remain in situ following attempt at manual removal, a patient may require surgical management. In a study of >20,000 patients in Norway, 3% of women requiring manual removal of retained placenta needed additional surgical management with dilation and curettage.[17] Another case–control study of 114 women found that cases required more dilation and curettage than controls, although with their study number they could not confirm significance.[18] Occasionally portions of the placenta or membranes may remain in the uterus after manual extraction, leading to delayed complications from retained products of conception. These can include delayed postpartum hemorrhage or endomyometritis.

Evidence of infection risk, particularly endometritis, following manual or surgical removal of retained placenta has been inconsistently demonstrated.[20] A large 1995 retrospective cohort study at University of Iowa compared over 1000 patients requiring manual extraction after vaginal delivery with those who did not.[20] After controlling for confounders, the authors found that manual removal of retained placenta was significantly associated with postpartum endometritis.[20] Alternatively, in the large cohort study of >20,000 patients from Norway mentioned above, patients requiring intervention for retained placenta did not show a significantly increased risk of infection, despite varying practices regarding antibiotic administration and timing.[17] Other studies have similarly found a relationship but could not prove a significant association between manual removal or surgical placental removal and endometritis.[18,21] The discrepancies may in part be due to the lack of rigorous distinction between postpartum fever and true uterine infection.

Diagnosis

Retained placenta is clinically diagnosed when the placenta fails to spontaneously separate during the third stage of labor, with or without active management, or in the setting of severe bleeding in the absence of placental delivery.[18,22] The first diagnostic criterion requires a time cutoff, though there is no uniform consensus as to timing for diagnosis of retained placenta in the third stage in the absence of postpartum hemorrhage. Selection of a clinical time definition can be based either on a population curve of observed spontaneous placental delivery times or on a time at which morbidity significantly increases. Thirty minutes have been used as a loose guideline, which comes from a 1991 study by Combs et al.[2] The researchers

found that the third stage had a log-normal distribution, with a mean length of 6.8 minutes, with only 3.3% of deliveries having greater a greater than 30 minutes third stage. This timing has been supported by other studies as well.[8] Interestingly, the authors calculated that the incidence of PPH, transfusion, and dilation and curettage remained constant during this period, increasing only after 30 minutes and plateauing at 75 minutes for both manually and spontaneously delivered placentas. Because PPH incidence did not increase until after 30 minutes, Combs et al recommended this timing for initiation of manual removal of the placenta.

However, this guidance is not uniformly supported. In a subsequent study by Deneux-Tharaux, surveys from 14 European countries exhibited wide variations in wait time prior to manual placental removal, largely by country but also by the hospital.[23] In countries such as Finland and Denmark, obstetricians tended to wait 60 minutes or more prior to manual removal of the placenta, versus in countries such as Spain and France, where providers removed the placenta after 30 minutes. Practices also varied considerably depending on whether or not the patient in question had prior epidural anesthesia.[23] National and worldwide guidelines similarly have no consensus on when to intervene on an undelivered placenta. For instance, the National Institute for Health and Clinical Excellence suggests a wait time of 30 minutes in the United Kingdom prior to manual removal of the placenta,[24] while the World Health Organization guidelines propose a wait time of 60 minutes.[12,25]

The most significant risk of waiting a prolonged amount of time before removing the placenta is postpartum hemorrhage. In 2005, Magann and colleagues undertook a prospective observational study in which all women delivering vaginally were assessed for PPH.[15] Using receiver operating characteristic curves, the authors showed that 95% of normal placental delivery occurs within 18 minutes, and that a third stage of labor longer than 18 minutes was associated with a significant risk of PPH.[19] The authors followed up this paper in 2012 with a randomized controlled trial assigning vaginal deliveries to manual removal at either 10 or 15 minutes (as opposed to the traditional 30) if the placenta had not yet spontaneously delivered.[26] The findings supported the authors' initial study, showing that removal at 15 minutes had a significantly greater likelihood of hemorrhage compared to 10 minutes, opening up the discussion on earlier intervention.[26]

At times the bulk of the placenta will deliver spontaneously or manually, but small portions or an accessory lobe may be retained. This may be suspected when the placenta appears fragmented after delivery or when there is ongoing heavy uterine bleeding. In this situation, the uterine cavity may be evaluated with manual exploration or with ultrasound. The utility of ultrasound in this situation has yet to be established, with a focal endometrial mass, particularly with Doppler flow, being the findings of interest. In one study of routine ultrasound immediately after vaginal delivery, the sensitivity for diagnosing retained placental fragments was only 44% with a positive predictive value (PPV) of 58%.[27] An alternate study showed a 75–80% sensitivity of postpartum ultrasound, though the mean time for evaluation was 21 days postpartum, when less blood and decidua are expected to be seen.[28] While immediate ultrasound's PPV will be higher when there is clinical suspicion of retained POCs, a negative ultrasound should not deter manual or suction curettage when there is a strong clinical suspicion, especially in the setting of hemorrhage.

Management

After delivery of the infant and prior to diagnosis of retained placenta, active management is recommended to facilitate spontaneous placental separation, including oxytocin, controlled cord traction, and uterine massage.[4] These maneuvers have been shown to decrease the risk of postpartum hemorrhage, though it has not been shown that active management will prevent retained placenta.[22]

Once diagnosed, the placenta is usually manually extracted from the uterus.[22,29] Table 2 lists items that should be readily available if needed during the extraction process. Because this procedure is painful, adequate analgesia should be achieved via epidural, conscious sedation, or general anesthesia prior to an attempt at extraction. Once the patient is comfortable, she should be appropriately positioned in lithotomy. A conical drape, preferably one that is graduated and marked to allow for quantitative blood loss, should be placed under the patient's buttocks. The operator should make every attempt to wear gown and gloves and maintain sterility, both for personal and for patient protection. The patient's bladder should be drained. The provider should then use one hand to follow the umbilical cord through the vagina and cervix until the placenta is palpated. If the placenta is separated but not expelled, such as in the case of uterine atony, the tissue can be firmly grasped and brought through the cervix.

Table 2 Items that should be available for manual placental extraction

Medications
Analgesics or sedatives with appropriate monitoring equipment Uterotonic agents Nitroglycerin
Patient preparation
Conical under-buttocks drape for blood collection Bladder catheter
Surgical instruments
Sponge forceps for grasping tissue Long curette
Hemorrhage management
Intrauterine balloon or uterine packing material Availability of crossmatched blood Massive transfusion protocol Equipment for quantitative blood loss measurement (volumetric or gravimetric) Available operating room with anesthesia equipment Suction curettage equipment Laparotomy equipment

Uterotonic medications, such as oxytocin, methylergonovine, carboprost, or other prostaglandins, should be given to facilitate contraction once the placenta is removed.[4]

Nitroglycerine (NTG) has been used to facilitate manual extraction by relaxing uterine smooth muscle.[30] This may be particularly helpful when the placenta is trapped behind a partially closed cervix, though the use of NTG alone does not appear to facilitate spontaneous placental expulsion.[31] It can be given as a 1 mg sublingual dose, or as sequential 50 mcg intravenous boluses, up to a total dose of 200 mcg. The medication can produce hypotension and tachycardia, which can confound assessments of maternal stability. Once the placenta is delivered, uterotonics should be promptly given to restore uterine tone and avoid significant atony.

If the placenta remains attached to the uterine decidua, an attempt should be made to separate it manually. Using one hand to provide counter pressure on the fundus through the maternal abdomen, the provider should then use the internal hand to manually create a cleavage plane between the placenta with the attached decidua and the myometrium. Once separated, the placenta can be removed as described above. If a separation plane cannot be created behind all or part of the placenta, the provider should suspect a morbidly adherent placenta (MAP) and prepare for potential hemorrhage.

If placental removal is refractory or only partially successful (ie the placenta or parts of the placenta remain in the uterus), or if bleeding persists despite placental delivery, often the next step is surgical management with curettage. This may be best achieved in an operating room, with optimal access to surgical equipment, analgesia, and patient resuscitation aids, if needed. Suction curettage is generally used, though a sharp curette may be needed to facilitate a separation plane. Access to uterine tamponade supplies with either a large intrauterine balloon or surgical packs should be immediately accessed in the event of hemorrhage. Crossmatched blood products should be made imminently available if placental separation is difficult or blood loss exceeds 1 L, and the care team should attend to uterotonic administration and attention to coagulopathy as the extraction is performed.[4]

Due to the risk of endometritis, routine antibiotics are generally administered just before or shortly after manual removal of the placenta.[20] Prophylaxis can parallel cesarean prophylaxis with a first-generation cephalosporin. Patients who are febrile at the time of extraction should be fully treated for chorioamnionitis with broad-spectrum antibiotics.[32] Despite these guidelines, few studies have been undertaken examining the effectiveness of antibiotics in reducing infectious morbidity. A 2015 systematic review by Chibueze and colleagues attempted to summarize the literature on the efficacy of antibiotics for preventing adverse maternal outcomes related to manual placenta removal following vaginal birth.[21] The authors reported on three retrospective cohort studies examining endometritis and puerperal fever after manual extraction for retained placenta. None of the three studies found evidence to suggest beneficial effects for routine antibiotic use in women undergoing intervention for retained placenta. The authors concluded that further research is required to adequately answer this question.[21] Due to mixed data regarding prophylaxis, as well as the increasing risk of postpartum hemorrhage with prolonged third stage of labor, administration of antibiotics should not delay manual removal of retained placenta.

Occasionally, a portion of placental tissue may remain in the uterus, either knowingly or unbeknownst to the providers. This can present as abnormal bleeding days to weeks after delivery and should be suspected in the setting of a delayed postpartum hemorrhage. Recently, studies have examined the usefulness of hysteroscopic morcellation devices in aiding with retained placenta left in situ postpartum (Figure 1A [before] and B [after]). In a series

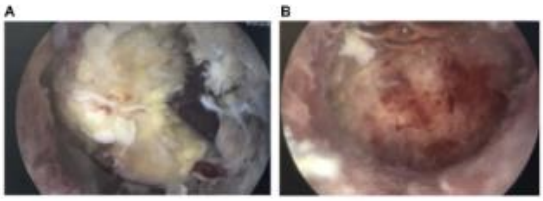

Figure 1 The photo on the left (**A**) shows a retained portion of placenta approximately 8 weeks after delivery. The photo on the right (**B**) shows the same uterus following hysteroscopic morcellation of the retained placenta.

of case reports, Lee and colleagues reported a higher risk of complications with blind curettage compared to hysteroscopic morcellation.[33] They additionally reported complete resection in 90% of hysteroscopic cases and reduction of both perforation and intrauterine adhesion risk.[33] In another randomized control trial by Hamerlynck et al, the authors randomized patients to undergo hysteroscopic resection of retained placenta with either hysteroscopic morcellation versus loop resection with rigid bipolar resectoscopes.[34] These authors in comparison found that when comparing the two modalities, complete resection was comparatively high in both groups, and intrauterine adhesions were comparatively low.[34] The one significant difference between the two groups was that the hysteroscopic group had significantly faster operative times.[34] The ability to perform hysteroscopic removal depends on the amount of active bleeding, with suction curettage often needed when bleeding is heavy.

Other studies have examined alternative, nonsurgical, management for retained placenta, none of which have been successful. In 2012, 99 women in a large teaching hospital in the Netherlands with retained placenta (>60 mins after delivery) were given either 800 mcg misoprostol or placebo orally.[35] The author's primary outcomes were number of manual removals of retained placenta and blood loss. The authors found that oral misoprostol reduced neither the need for manual removal nor the overall amount of blood loss. Both groups were observed for additional 45 mins after administration of misoprostol or placebo. While the authors found that 50% of remaining placentas at 60 mins delivered in the intervening 45 mins, it came at the expense of additional significant blood loss.[35]

For a time, umbilical vein oxytocin was thought to be a promising alternative or adjunct to manual extraction of the placenta. A 2011 Cochrane Review summarized available data on the subject to assess the use of umbilical vein oxytocin either alone or in conjunction with intravenous oxytocin to reduce the need for manual removal of retained placenta.[36] While inexpensive and easy to do, the authors found that all well-designed randomized control trials showed no significant effect of umbilical vein oxytocin on retained placenta.[36]

Morbidly adherent placenta

In the unusual event that manual extraction does not result in delivery of the entire or partial placenta, MAP must be considered as an etiology. The PAS, which includes accreta, increta, or percreta, can be causes of significant surgical and hemorrhagic morbidity on the labor and delivery floor[4,37] (Figure 2). While PAS is relatively rare, particularly in the absence of a placenta previa, it can occur at vaginal delivery when there is no previa. Given

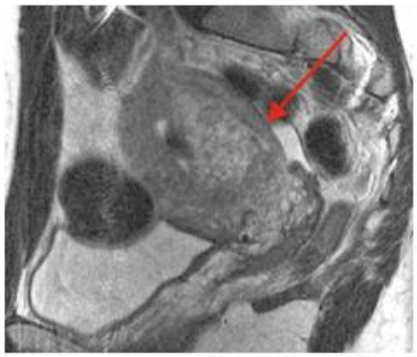

Figure 2 Magnetic resonance image showing a portion of retained placenta 6 weeks postpartum. The arrow indicates an area where the light-gray placenta is deeply invasive into the darker-gray myometrium. Placenta accreta spectrum was confirmed pathologically following hysterectomy.

the excess morbidity, providers should consider this pathology when a placenta is retained in the setting of significant PAS risk factors. These include prior uterine surgeries, including hysteroscopic resections, IVF conception, a history of intrauterine adhesions, or a prior history of MAP or pathologic findings of accreta.[38,39]

When a separation plane cannot be created or extraction attempts begin to invert the uterus, MAP should be suspected. In this case, further attempts to extract the placenta should cease, as forcible removal of a MAP can lead to massive hemorrhage.[40] At this point, consideration should be made for hysterectomy, which will be necessary if the patient has an undeliverable placenta with significant hemorrhage. Alternative treatment has been described including expectant management or uterine conservation.[41] Expectant management has been described in small studies and refers to the placenta left in situ after diagnosis of PAS.[38,41,42] Such management requires careful patient selection and counseling, as this risks delayed hemorrhage or infection. Nevertheless, successful conservative management has been described, with placental expulsion, resorption, or removal at a median of 3 months and up to 1 year postpartum.[43]

Uterine conservation with placental removal is an alternative technique that likewise has been described in only small studies. This refers to resection of the placental bed at the area of suspected PAS and requires conversion to laparotomy after vaginal delivery.[41] The resultant defect in theory can be repaired via over-sewing and/or uterine repair or alternatively attempting tamponade with a Bakri balloon. Only one small study has evaluated the latter in a randomized control trial, and only with the lesser invasive types of PAS.[41,44]

Conclusion

Retained placenta after vaginal delivery can be a source of significant hemorrhagic and surgical morbidity to the mother. In considering ways to lesson morbidity, the clinician should have a knowledge of risk factors for both retained placenta and MAP, allowing them to triage those patients most at risk of hemorrhage and prepare by ensuring blood products are easily available. When managing the patient with retained placenta, 30 minutes of elapsed third stage have been traditionally used as a guideline for timing manual removal; however, recent research has suggested that shorter duration of third stage may in fact be less morbid. Further research should be pursued to determine the best timing and infection prophylaxis for this etiology. Regardless, prompt diagnosis and management with appropriate personnel, access to blood for massive transfusion protocol, and surgical equipment such as uterine suction and tamponade can be required to treat retained placenta and lessen its morbidity.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Dombrowski MP, Bottoms SF, Saleh AA, Hurd WW, Romero R. Third stage of labor: analysis of duration and clinical practice. *Am J Obstet Gynecol*. 1995;172(4 Pt 1):1279–1284. doi:10.1016/0002-9378(95)91493-5
2. Combs CA, Murphy EL, Laros RK. Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol*. 1991;77(1):69–76.
3. Nikolajsen S, Løkkegaard ECL, Bergholt T. Reoccurrence of retained placenta at vaginal delivery: an observational study. *Acta Obstet Gynecol Scand*. 2013;92(4):421–425. doi:10.1111/j.1600-0412.2012.01520.x
4. American College of Obstetricians and Gynecologists. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists number 76, October 2006: postpartum hemorrhage. *Obstet Gynecol*. 2006;108(4):1039–1047. doi:10.1097/01.AOG.0000214671.19023.68
5. Endler M, Grünewald C, Saltvedt S. Epidemiology of retained placenta: oxytocin as an independent risk factor. *Obstet Gynecol*. 2012;119(4):801–809. doi:10.1097/AOG.0b013e31824acb3b
6. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg*. 2010;110(5):1368–1373.
7. Kraus FT, Redline RW, Gersell DJ, Nelson DM, Dicke JM. Placental Pathology. American Registry of Pathology in collaboration with the Armed Forces Institute of Pathology. *Atlas Nontumor Pathol*. 2004;1:10–16.
8. Urner F, Zimmermann R, Krafft A. Manual removal of the placenta after vaginal delivery: an unsolved problem in obstetrics. *J Pregnancy*. 2014;2014:274651. doi:10.1155/2014/239406
9. Greenbaum S, Wainstock T, Dukler D, Leron E, Erez O. Underlying mechanisms of retained placenta: evidence from a population based cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2017;216:12–17. doi:10.1016/j.ejogrb.2017.06.035
10. Kramer MS, Berg C, Abenhaim H, et al. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. *Am J Obstet Gynecol*. 2013;209(5):449.e1–7. doi:10.1016/j.ajog.2013.07.007
11. Endler M, Saltvedt S, Cnattingius S, Stephansson O, Wikström A-K. Retained placenta is associated with pre-eclampsia, stillbirth, giving birth to a small-for-gestational-age infant, and spontaneous preterm birth: a national register-based study. *BJOG Int J Obstet Gynaecol*. 2014;121(12):1462–1470. doi:10.1111/1471-0528.12752
12. Joseph KS, Rouleau J, Kramer MS, et al. Investigation of an increase in postpartum haemorrhage in Canada. *BJOG Int J Obstet Gynaecol*. 2007;114(6):751–759. doi:10.1111/j.1471-0528.2007.01316.x
13. Endler M, Cnattingius S, Granfors M, Wikström A-K. The inherited risk of retained placenta: a population based cohort study. *BJOG Int J Obstet Gynaecol*. 2018;125(6):737–744. doi:10.1111/1471-0528.14828
14. Esh-Broder E, Ariel I, Abas-Bashir N, Bdolah Y, Celnikier DH. Placenta accreta is associated with IVF pregnancies: a retrospective chart review. *BJOG Int J Obstet Gynaecol*. 2011;118(9):1084–1089. doi:10.1111/j.1471-0528.2011.02976.x
15. Elenis E, Svanberg AS, Lampic C, Skalkidou A, Åkerud H, Sydsjö G. Adverse obstetric outcomes in pregnancies resulting from oocyte donation: a retrospective cohort case study in Sweden. *BMC Pregnancy Childbirth*. 2015;8(15):247. doi:10.1186/s12884-015-0687-9

16. Aziz MM, Guirguis G, Maratto S, Benito C, Forman EJ. Is there an association between assisted reproductive technologies and time and complications of the third stage of labor? *Arch Gynecol Obstet*. 2016;293(6):1193–1196. doi:10.1007/s00404-015-3943-3
17. Tandberg A, Albrechtsen S, Iversen OE. Manual removal of the placenta. Incidence and clinical significance. *Acta Obstet Gynecol Scand*. 1999;78(1):33–36. doi:10.1080/j.1600-0412.1999.780108.x
18. Titiz H, Wallace A, Voaklander DC. Manual removal of the placenta–a case control study. *Aust N Z J Obstet Gynaecol*. 2001;41(1):41–44. doi:10.1111/ajo.2001.41.issue-1
19. Magann EF, Evans S, Chauhan SP, Lanneau G, Fisk AD, Morrison JC. The length of the third stage of labor and the risk of postpartum hemorrhage. *Obstet Gynecol*. 2005;105(2):290–293. doi:10.1097/01.AOG.0000159040.51773.bf
20. Ely JW, Rijhsinghani A, Bowdler NC, Dawson JD. The association between manual removal of the placenta and postpartum endometritis following vaginal delivery. *Obstet Gynecol*. 1995;86(6):1002–1006. doi:10.1016/0029-7844(95)00327-N
21. Chibueze EC, Parsons AJQ, Ota E, Swa T, Oladapo OT, Mori R. Prophylactic antibiotics for manual removal of retained placenta during vaginal birth: a systematic review of observational studies and meta-analysis. *BMC Pregnancy Childbirth*. 2015;26(15):313. doi:10.1186/s12884-015-0752-4
22. Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. *Lancet Lond Engl*. 1998;351(9104):693–699. doi:10.1016/S0140-6736(97)09409-9
23. Deneux-Tharaux C, Macfarlane A, Winter C, et al. Policies for manual removal of placenta at vaginal delivery: variations in timing within Europe. *BJOG Int J Obstet Gynaecol*. 2009;116(1):119–124. doi:10.1111/j.1471-0528.2008.01996.x
24. National Collaborating Centre for Women's and Children's Health (UK). *Intrapartum Care: Care of Healthy Women and Their Babies during Childbirth* [internet]. London: RCOG Press; 2007 [cited Jun 2, 2019] (National Institute for Health and Clinical Excellence: Guidance). Available from: http://www.ncbi.nlm.nih.gov/books/NBK49388/. Accessed September 3, 2019.
25. Ronsmans C, Graham WJ; Lancet Maternal Survival Series steering group. Maternal mortality: who, when, where, and why. *Lancet Lond Engl*. 2006;368(9542):1189–1200. doi:10.1016/S0140-6736(06)69380-X
26. Magann EF, Niederhauser A, Doherty DA, Chauhan SP, Sandlin AT, Morrison JC. Reducing hemodynamic compromise with placental removal at 10 versus 15 mins: a randomized clinical trial. *Am J Perinatol*. 2012;29(8):609–614. doi:10.1055/s-0032-1311985
27. Carlan SJ, Scott WT, Pollack R, Harris K. Appearance of the uterus by ultrasound immediately after placental delivery with pathologic correlation. *J Clin Ultrasound*. 1997;25(6):301–308. doi:10.1002/(SICI)1097-0096(199707)25:6<301::AID-JCU3>3.0.CO;2-G
28. Durfee SM, Frates MC, Luong A, Benson CB. The sonographic and color Doppler features of retained products of conception. *J Ultrasound Med Off J Am Inst Ultrasound Med*. 2005;24(9):1181–6; quiz 1188–9.
29. Rogers MS, Yuen PM, Wong S. Avoiding manual removal of placenta: evaluation of intra-umbilical injection of uterotonics using the Pipingas technique for management of adherent placenta. *Acta Obstet Gynecol Scand*. 2007;86(1):48–54. doi:10.1080/00016340601088570
30. Chedraui PA, Insuasti DF. Intravenous nitroglycerin in the management of retained placenta. *Gynecol Obstet Invest*. 2003;56(2):61–64. doi:10.1159/000072734
31. Abdel-Aleem H, Abdel-Aleem MA, Shaaban OM. Nitroglycerin for management of retained placenta. *Cochrane Database Syst Rev*. 2015;12(11):CD007708.
32. Committee on Obstetric Practice. Committee opinion no. 712: intrapartum management of intraamniotic infection. *Obstet Gynecol*. 2017;130(2):e95–101. doi:10.1097/AOG.0000000000002236
33. Lee MHM. Surgical management of retained placental tissue with the hysteroscopic morcellation device. *Gynecol Minim Invasive Ther*. 2019;8(1):33–35. doi:10.4103/GMIT.GMIT_66_18
34. Hamerlynck TWO, van Vliet HAAM, Beerens A-S, Weyers S, Schoot BC. Hysteroscopic morcellation versus loop resection for removal of placental remnants: a randomized trial. *J Minim Invasive Gynecol*. 2016;23(7):1172–1180. doi:10.1016/j.jmig.2016.08.828
35. van Stralen G, Veenhof M, Holleboom C, van Roosmalen J. No reduction of manual removal after misoprostol for retained placenta: a double-blind, randomized trial. *Acta Obstet Gynecol Scand*. 2013;92(4):398–403. doi:10.1111/aogs.12065
36. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. *Cochrane Database Syst Rev*. 2011;11(5):CD001337.
37. Bjurström J, Collins S, Langhoff-Roos J, et al. Failed manual removal of the placenta after vaginal delivery. *Arch Gynecol Obstet*. 2018;297(2):323–332. doi:10.1007/s00404-017-4579-2
38. Carusi DA. The placenta accreta spectrum: epidemiology and risk factors. *Clin Obstet Gynecol*. 2018;61(4):733–742.
39. Roeca C, Little SE, Carusi DA. Pathologically diagnosed placenta accreta and hemorrhagic morbidity in a subsequent pregnancy. *Obstet Gynecol*. 2017;129(2):321–326. doi:10.1097/AOG.0000000000001843
40. Kayem G, Davy C, Goffinet F, Thomas C, Clément D, Cabrol D. Conservative versus extirpative management in cases of placenta accreta. *Obstet Gynecol*. 2004;104(3):531–536. doi:10.1097/01.AOG.0000136086.78099.0f
41. Placenta accreta spectrum. Obstetric care consensus no. 7. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2018;132:e259–e275. doi:10.1097/AOG.0000000000002983
42. Fox KA, Shamshirsaz AA, Carusi D, et al. Conservative management of morbidly adherent placenta: expert review. *Am J Obstet Gynecol*. 2015;213(6):755–760. doi:10.1016/j.ajog.2015.04.034
43. Sentilhes L, Ambroselli C, Kayem G, et al. Maternal outcome after conservative treatment of placenta accreta. *Obstet Gynecol*. 2010;115(3):526–534. doi:10.1097/AOG.0b013e3181d066d4
44. Pala S, Atilgan R, Başpınar M, et al. Comparison of results of Bakri balloon tamponade and caesarean hysterectomy in management of placenta accreta and increta: a retrospective study. *J Obstet Gynaecol J Inst Obstet Gynaecol*. 2018;38(2):194–199. doi:10.1080/01443615.2017.1340440

frontiers in Physiology

REVIEW
published: 25 July 2018
doi: 10.3389/fphys.2018.00973

Preeclampsia: Novel Mechanisms and Potential Therapeutic Approaches

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Preeclampsia is a serious complication of pregnancy where it affects 5–8% of all pregnancies. It increases the morbidity and mortality of both the fetus and pregnant woman, especially in developing countries. It deleteriously affects several vital organs, including the kidneys, liver, brain, and lung. Although, the pathogenesis of preeclampsia has not yet been fully understood, growing evidence suggests that aberrations in the angiogenic factors levels and coagulopathy are responsible for the clinical manifestations of the disease. The common nominator of tissue damage of all these target organs is endothelial injury, which impedes their normal function. At the renal level, glomerular endothelial injury leads to the development of maternal proteinuria. Actually, peripheral vasoconstriction secondary to maternal systemic inflammation and endothelial cell activation is sufficient for the development of preeclampsia-induced hypertension. Similarly, preeclampsia can cause hepatic and neurologic dysfunction due to vascular damage and/or hypertension. Obviously, preeclampsia adversely affects various organs, however it is not yet clear whether pre-eclampsia *per se* adversely affects various organs or whether it exposes underlying genetic predispositions to cardiovascular disease that manifest in later life. The current review summarizes recent development in the pathogenesis of preeclampsia with special focus on novel diagnostic biomarkers and their relevance to potential therapeutic options for this disease state. Specifically, the review highlights the renal manifestations of the disease with emphasis on the involvement of angiogenic factors in vascular injury and on how restoration of the angiogenic balance affects renal and cardiovascular outcome of Preeclamptic women.

Keywords: preeclampsia, maternity, fetus, endothelium, kidney, placental growth factor (PlGF), soluble growth factor receptor-sFlt, endoglin

OPEN ACCESS

Edited by:
Elke Winterhager,
Universität Duisburg-Essen, Germany

Reviewed by:
Reecha Sharma,
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Graham Burton,
University of Cambridge, United Kingdom

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Specialty section:
This article was submitted to Reproduction, a section of the journal Frontiers in Physiology

Received: *05 March 2018*
Accepted: *02 July 2018*
Published: *25 July 2018*

Citation:
Armaly Z, Jadaon JE, Jabbour A and Abassi ZA (2018) Preeclampsia: Novel Mechanisms and Potential Therapeutic Approaches. Front. Physiol. 9:973. doi: 10.3389/fphys.2018.00973

INTRODUCTION

Preeclampsia (PE) is a profound complication of pregnancy, where it affects 3–8% of all pregnancies and dramatically increases the risk of all-cause mortality, especially in women who experienced early, severe, preterm episode (Backes et al., 2011; Jim and Karumanchi, 2017). Preeclampsia negatively affects both the mother and fetus (**Table 1**). Concerning the

latter, preeclampsia may cause intra-uterine fetal growth restriction (IUGR), placental abruption, preterm delivery and associated complications including, neonatal respiratory distress syndrome, cerebral palsy, necrotizing enterocolitis retinopathy of prematurity and even perinatal death (**Table 1**; Backes et al., 2011). Besides its deleterious impact on the fetus, preeclampsia also affects the pregnant woman, where it is associated with hypertension, kidney damage, liver injury/failure, central nervous system (CNS) damage, stroke, cardiomyopathy, pulmonary edema, adult respiratory distress syndrome, and even death (**Table 1**; Berg et al., 1996; Vikse et al., 2008; Ghulmiyyah and Sibai, 2012). Actually, preeclampsia is responsible for more than 60,000 maternal deaths annually worldwide, placing it as the third cause of maternal mortality after bleeding and embolism (Mongraw-Chaffin et al., 2010; Young et al., 2010). Higher mortality rate was observed when preeclampsia is associated with HELLP (hemolysis, elevated liver enzymes, low platelets), syndrome liver hemorrhage or rupture, acute kidney injury (AKI), oliguria, disseminated intravascular coagulation (DIC), and pulmonary edema (Ghulmiyyah and Sibai, 2012). Preeclampsia is of special relevance in the developing countries, where the maternal mortality is ~15% compared with 0–1.8% in the developed countries (Ghulmiyyah and Sibai, 2012). This difference is largely attributed to inadequate perinatal care in poor regions of the world, and subsequently missing timely detection of hypertension, generalized or local edema, and proteinuria to detect preeclampsia at early stages.

In the last decade, the definition of preeclampsia was revisited as the mechanisms underlying the disease were dramatically evolved. Concerning the former, several leading groups have challenged the half century old classic definition of preeclampsia, namely, *de novo* hypertension, new onset of proteinuria and liver dysfunction after mid pregnancy, motivated by the discovery of additional biomarkers of preeclampsia (Tjoa et al., 2007; Staff et al., 2013; Palomaki et al., 2015; Baltajian et al., 2016). In this context, several studies have suggested to modernize the definition by incorporating key biomarkers of either placental or vascular origins, including placenta growth factor (PlGF) and antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFLT1) or soluble endoglin (sENG) in the diagnosis of preeclampsia and the risk for developing the disease and even in predicting the outcome (Tjoa et al., 2007; Staff et al., 2013; March et al., 2015; Palomaki et al., 2015; Sircar et al., 2015; Baltajian et al., 2016). The suggested definition takes into account the impressive advancement in understanding the pathophysiology of preeclampsia and the mechanism-based novel diagnostics and therapeutic options.

In light of the rapid pace in the development of this issue and its clinical relevance, the current review concentrates on recent breakthroughs in diagnosing preeclampsia and the derived therapeutic options, which are currently been tested in advanced clinical trials. The initial results seem encouraging and may break down the old dogma claiming that no intervention has been proved to prevent or delay the onset of preeclampsia and the only effective treatment is delivery.

TABLE 1 | Adverse impact of preeclampsia on fetus and mother.

On fetus	On mother
• Growth restriction	• Hypertension
• Preterm delivery	• Future HTN, CVD
• Placental abruption	• Kidney injury
• Respiratory distress	• Chronic kidney disease and risk for ESRD
• Cerebral palsy	• Liver failure
• Retinopathy of prematurity	• Cardiomyopathy
• Necrotizing enterocolitis	• CNS damage and stroke
• Sepsis	• Seizure
• Stillbirth	• Diabetes mellitus
	• Coronary artery disease
	• Pulmonary edema
	• Death

RISK FACTORS FOR PREECLAMPSIA

Although the mechanisms of preeclampsia are poorly elucidated, there are several predisposing factors that increase the risk for the development of the disease (**Table 2**; Al-Jameil et al., 2014). Among the leading risk factors (yet uncommon) is antiphospholipid antibody syndrome (APLA-S). In addition, numerous epidemiological studies have demonstrated that chronic kidney disease (CKD) significantly increases the risk of preeclampsia, especially lupus (Roberts et al., 1989; Mostello et al., 2002; Clowse et al., 2008; Jim and Karumanchi, 2017). Risk factors for pre-eclampsia include also former preeclampsia, first pregnancy, obesity, pregestational hypertension, older age, and diabetes mellitus (Al-Jameil et al., 2014). It is also more frequent in multifetal pregnancy, where the incidence of preeclampsia

TABLE 2 | Major predisposing risk factors for the development of preeclampsia.

Risk factor	OR or RR (95% CI)
Antiphospholipid antibody syndrome	9.7 (4.3–21.7)
Renal disease	7.8 (2.2–28.2)
Prior preeclampsia	7.2 (5.8–8.8)
Systemic lupus erythmatosis	5.7 (2.0–16.2)
Nulliparity	5.4 (2.8–10.3)
HIV+ HAART treatment	5.6 (1.7–18.1)
HIV positive (untreated)	4.9 (2.4–10.1)
Chronic hypertension	3.8 (3.4–4.3)
Diabetes Mellitus	3.6 (2.5–5.0)
Multiple Gestation	3.5 (3.0–4.2)
Strong family history of cardiovascular disease (heart disease or stroke in ≥2 first degree relatives)	3.2 (1.4–7.7)
Obesity	2.5 (1.7–3.7)
Family history of preeclampsia in first degree relative	2.3–2.6 (1.8–3.6)
Advanced maternal age (>40) for multips	1.96 (1.34–2.87)
Advanced maternal age (>40) for nulliparas	1.68 (1.23–2.29)

is increased in twin compared to singleton pregnancies to 6–31% (McFarlane and Scott, 1976; Coonrod et al., 1995). Despite the association between these risk factors and preeclampsia, the mechanisms whereby these factors increase this risk are largely unknown. However, underlying diseases characterized by imbalance of angiogenetic factors and coagulation may explain why certain populations are at risk. Despite that, in most cases preeclampsia is unpredictable (Jim and Karumanchi, 2017).

PATHOGENESIS OF PREECLAMPSIA

In the last decade, our understanding of the pathogenesis of preeclampsia has progressively advanced (Phipps et al., 2016). Therefore, in this section we will focus on the most recent concepts in the pathogenesis of the disease, especially the involvement of angiogenic factors. It is obvious today that preeclampsia is a systemic disease characterized by generalized endothelial damage (Roberts et al., 1989), thus negatively affecting almost all organs of preeclamptic women, including the potential to affect future cardiovascular and renal diseases even decades after the disease occurrence (**Figure 1**; Berg et al., 1996; Vikse et al., 2008). In this context, a comprehensive prospective study revealed that preeclampsia was independently associated with cardiovascular disease death (mutually adjusted hazard ratio: 2.14 [95% CI: 1.29–3.57]) (Mongraw-Chaffin et al., 2010). The situation was even grimmer in women who experienced preeclampsia by 34 weeks of gestation (HR, 9.54; 95% CI, 4.50–20.25) (Mongraw-Chaffin et al., 2010). The high mortality rate could be explained by the findings that early-onset preeclampsia conferred a substantially higher risk of cardiovascular, respiratory, CNS, renal, hepatic, and other morbidity and was evident by end target damage (Lisonkova et al., 2014). Collectively, these findings suggest that the risk of morbidity/mortality among preeclamptic women is related to the severity the disease and gestational age at onset, namely early (<34 weeks) or late (>34 weeks). However, it should be emphasized that if the mother has a genetic predisposition to cardiovascular disease, then it is this rather than pre-eclampsia *per se* that causes the increased morbidity in later life as outlined above. Therefore, additional studies are needed to distinguish between the contribution of preeclampsia itself and the genetics to the high prevalence of cardiovascular morbidity and mortality among preeclamptic women.

It is now appreciated that early- and late-onset pre-eclampsia have different pathophysiologies, thus advancing our understanding of the syndrome. In early-onset, also referred to as placental pre-eclampsia, there is clear evidence of reduced maternal spiral artery conversion in early pregnancy. This is associated with placental malperfusion, and gross and molecular pathology of the placental tissues. Oxidative stress of the placenta causes increased secretion of sFLT-1 and reduced PlGF, reflecting the biomarker patterns. In late-onset pre-eclampsia, called also maternal preeclampsia, there is little evidence of reduced arterial conversion and placental perfusion is maintained or even increased (Sohlberg et al., 2014). Thus, there is only minimal placental stress (Yung et al., 2005) so that sFLT and placental growth factor (PlGF) secretion by the placenta are close to the normal range. These cases, which represent nearly 80% of pre-eclampsia, are now thought to be due to a genetic maternal pre-disposition to cardiovascular disease, which manifests as pre-eclampsia during the stress-test of pregnancy.

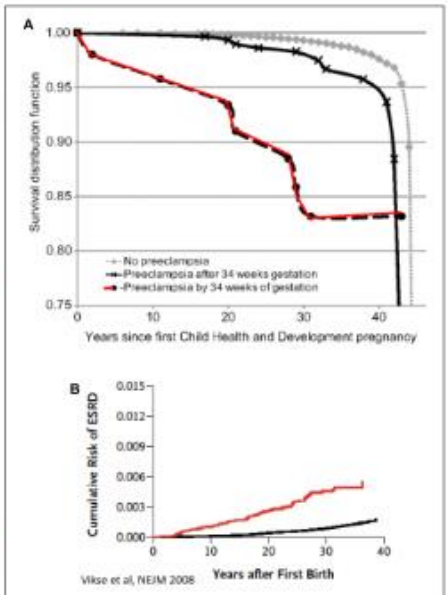

FIGURE 1 | (A) CVD death Kaplan–Meier survival according to gestational timing of preeclampsia. Survival analysis is based on 14, 403 pregnant women. A total of 481 had observed preeclampsia, and 266 died from cardiovascular disease (adopted with permission from Mongraw-Chaffin et al., 2010). **(B)** Cumulative risk of end-stage renal disease (ESRD) after first preeclampsia (adopted with permission from Vikse et al., 2008).

The pathology early-onset preeclampsia starts with abnormal formation of blood vessels in the maternal uterine spiral arteries. During normal pregnancy, major adaptive changes take place including spiral artery remodeling in the pregnant uterus aimed at decreasing maternal blood vessel resistance and subsequently increasing unteroplacental perfusion (Lyall, 2005). However, mathematical modeling shows that the remodeling has relatively little impact on uteroplacental perfusion, and is more concerned with reducing the velocity of inflow and ensuring constancy of blood flow (Burton et al., 2009).

These alterations in spiral arteries, namely high-capacitance low-pressure flow to the placenta, are essential for fetal nutrition. Spiral artery remodeling is achieved through invasion of trophoblasts and disappearance of the smooth muscle in the blood vessel wall (Kaufmann et al., 2003; Lyall, 2005;

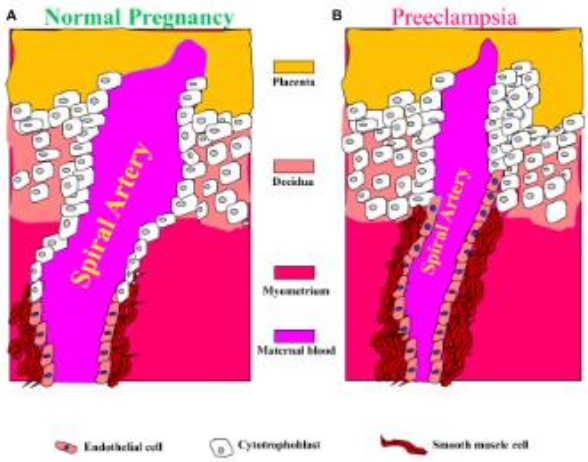

FIGURE 2 | Aberrant placentation and angiogenesis in preeclampsia. In normal pregnancy, cytotrophoblasts of fetal origin invade the maternal spiral arteries and replace endothelial cell layer. This action converts the spiral arteries from narrow highly resistant vessels to high-caliber capacitance vessels, which are capable of providing sufficient blood and nutrition supply to the fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial to an endothelial phenotype, a process referred to as pseudovasculogenesis, or vascular mimicry (**Right**). In preeclampsia, cytotrophoblasts fails to acquire invasive endothelial phenotype features, thus the invasion of the spiral arteries is inadequate leaving them narrow and highly resistant (**Left**). Modified with permission from Lam et al. (2005) and Powe et al. (2011).

Osol and Mandala, 2009). Using mouse model revealed that this process involves the full circumference of the vessel in its segment entering the placenta from the mesometrial triangle, so called, the central canal. The deeper parts of the spiral artery within the mesometrial triangle and even beyond it, as deep as the mesometrium, are only partially remodeled and retain the muscular wall in part of their circumference (Geusens et al., 2008; Skarzinski et al., 2009; **Figure 2**). In order to achieve spiral remodeling during normal pregnancy, many molecules including vasoactive substances, growth factors, adhesion molecules and proteases are secreted by the placenta and the vasculature (Brosens et al., 1972; Norwitz et al., 2001; Kaufmann et al., 2003; Lyall, 2005; Pijnenborg et al., 2006). Among the most famous representative substances in this context are vascular endothelial growth factor (VEGF), sFlt1, PlGF, and endoglin (Takimoto et al., 1996; Maynard et al., 2003; Levine et al., 2004; Li et al., 2005; Venkatesha et al., 2006; Kanasaki et al., 2008; Zhou et al., 2008). Furthermore, interactions with the maternal immune cells, especially uterine natural killer cells and their corresponding human leukocyte antigen-C (HLA-C) ligands on the invading trophoblast, are important for release of proteases and remodeling (Moffett et al., 2015). Interference with their central role in creating efficient uteroplacental interface and cardiovascular and renal adaptations during pregnancy contributes to preeclampsia as elaborated below. It is widely accepted that abrupt remodeling of the uterine spiral arteries plays a key role in the pathogenesis of early onset preeclampsia (Brosens et al., 1972; Norwitz et al., 2001; Kaufmann et al., 2003; Red-Horse et al., 2004; Pijnenborg et al., 2006), yet there is no evidence that they are involved in arterial remodeling of the spiral arteries.

Angiogenic Factors

As mentioned above, insufficient spiral artery remodeling due to superficial invasion of trophoblasts is the basis for the development of early-, but not late-onset cases of preeclampsia (Brosens et al., 1972; Norwitz et al., 2001; Kaufmann et al., 2003; Red-Horse et al., 2004; Pijnenborg et al., 2006). Perturbations in the generation of normal uteroplacental interface results in ischemic placenta and oxidative stress which stimulates the release of prohypertensive and anti-angiogenic factors (such as sFlt-1) (Cindrova-Davies, 2009). Moreover, sFlt-1 sensitizes the endothelial cells of the maternal circulation to pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) (Cindrova-Davies et al., 2011), causing generalized endothelial dysfunction and subsequently multisystem damage (**Figure 3**; Roberts et al., 1989; Llurba et al., 2015; Verdonk et al., 2015).

Placenta Growth Factor

Among these substances are VEGF sFlt1, PlGF, sENG, and endothelin (ET-1) (**Figure 3**; Llurba et al., 2015; Verdonk et al., 2015). Therefore, sFlt-1, PlGF and endoglin are

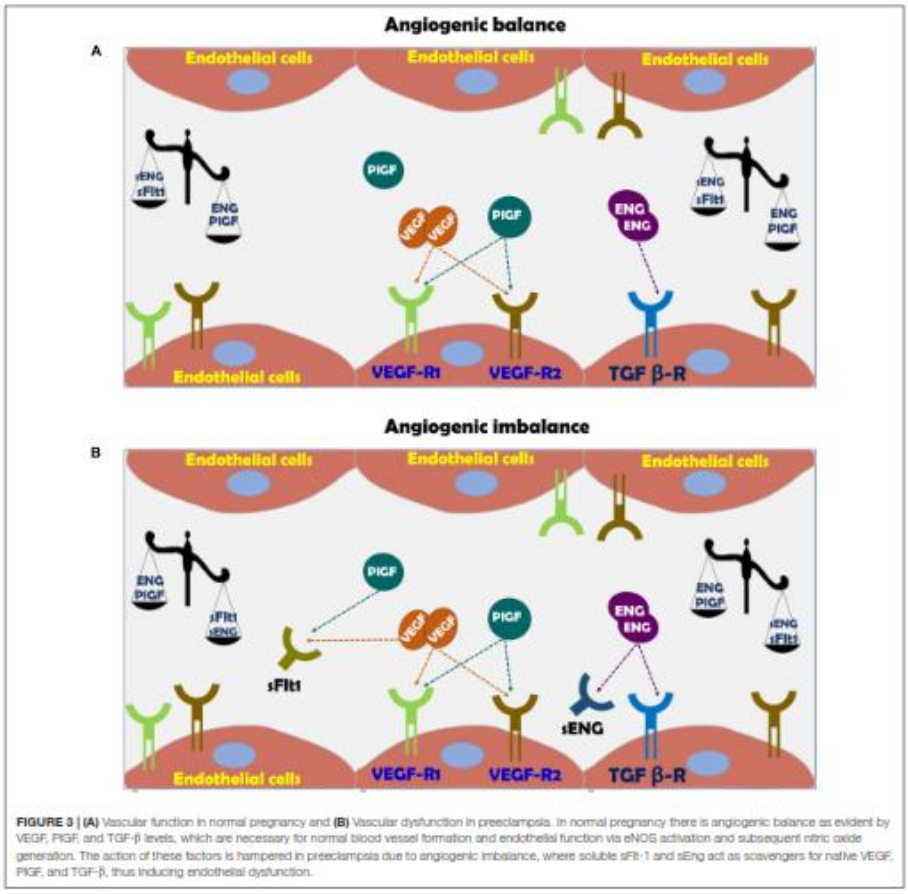

FIGURE 3 | (A) Vascular function in normal pregnancy and **(B)** Vascular dysfunction in preeclampsia. In normal pregnancy there is angiogenic balance as evident by VEGF, PlGF, and TGF-β levels, which are necessary for normal blood vessel formation and endothelial function via eNOS activation and subsequent nitric oxide generation. The action of these factors is hampered in preeclampsia due to angiogenic imbalance, where soluble sFlt-1 and sEng act as scavengers for native VEGF, PlGF, and TGF-β, thus inducing endothelial dysfunction.

extensively assessed as potential biomarkers for the diagnosis of preeclampsia (Venkatesha et al., 2006; Staff et al., 2013). While PlGF is proangiogenic, sFlt-1 is antiangiogenic factor (Ahmed, 2011). PlGF is expressed by the placenta, especially the syncytiotrophoblast (Maglione et al., 1991), but also by the endothelium (Staff et al., 2013). PlGF is a prominent angiogenic player in the development of the placental vascular system (Iwasaki et al., 2011; De Falco, 2012). During normal pregnancy, PlGF can be detected in the maternal circulation from 8 weeks gestation, reaching a maximal concentration toward the end of second trimester and declining thereafter until delivery (Taylor et al., 2003). In line with its proangiogenic function, reduced levels of PlGF were found in preeclampsia (George and Granger, 2010; Staff et al., 2013; Kar, 2014). It is noteworthy that infusion of recombinant human PlGF via intraperitoneal osmotic minipumps abolished the development of hypertension in experimental preeclampsia model (Spradley et al., 2016).

Soluble fms-Like Tyrosine Kinase-1

Vascular endothelial growth factor is critical for vascular homeostasis and activates both VEGF receptor-1 (VEGFR-1) and VEGFR-2 coupled to endothelial nitric oxide synthase (eNOS) required for angiogenesis (**Figure 3**; Ferrara, 2004; Ahmad et al., 2006; Sison et al., 2010; Bertuccio et al., 2011; Veron et al., 2012).

The importance of VEGF for the maintenance of normal endothelial function and development of placental vasculature is derived from the consequences of impairment of VEGF activity due to certain drugs or elevation of sFlt-1 (Ahmed, 1997; Kabbinavar et al., 2003; Sison et al., 2010; Bertuccio et al., 2011; Veron et al., 2012). In this context, anti-VEGF therapy with Avastin display preeclampsia-like symptoms, namely hypertension and proteinuria (Kabbinavar et al., 2003; Eremina et al., 2008; Muller-Deile and Schiffer, 2011; Hayman et al., 2014). sFlt-1 is a splice variant of VEGF receptor fms-like tyrosine kinase 1 (Maynard et al., 2003). sFlt-1 acts as a potent scavenger of VEGF- and PlGF, thus preventing their interaction with endothelial receptors on the cell surface and subsequently induces endothelial dysfunction (**Figure 3**; Kendall and Thomas, 1993; Levine et al., 2004). The elevation of sFlt-1 is due to overexpression of sFlt-1 mRNA as was demonstrated in *in vivo* and *in vitro* models of human placental hypoxia mediated by hypoxia inducible factor 1 (HIF-1) (Nevo et al., 2006; Onda et al., 2017). Support for its pro preeclamptic role came from experimental studies, where administration of adenoviral enhanced overexpression of sFlt-1 into pregnant rats or mice, induced clinical manifestations of preeclampsia, including profound elevation of blood pressure (BP), albuminuria, and renal histologic changes such as endotheliosis and fibrin deposition within the enlarged glomeruli (Gartner et al., 1998; Maynard et al., 2003; Onda et al., 2017). At the mechanistic level, sFlt-1 indirectly prevents the production of VEGF-induced NO, resulting in enhanced generation of reactive oxygen species and exaggerated vasoconstriction (Ahmad and Ahmed, 2004; Burke et al., 2016).

In clinical setting, sFlt-1 levels were found to be elevated as early as 5 weeks before the diagnosis of preeclampsia and directly correlate with disease severity (Levine et al., 2004; Kar, 2014). Furthermore, support for sFlt-1 role in the pathogenesis of preeclampsia is derived from experimental and clinical studies involving sFlt-1 elimination (Ahmad and Ahmed, 2004; Thadhani et al., 2016; Jim and Karumanchi, 2017). Specifically, sFlt-1 removal by dextran sulfate apheresis in humans reduced proteinuria and prolonged pregnancy (Thadhani et al., 2016).

Endoglin

Endoglin (ENG) is a type I membrane glycoprotein localized to the cell membrane where it constitutes the transmembrane co-receptor for TGF beta receptor complex (TGF-β1 and TGF-β3) (Gregory et al., 2014). ENG is expressed by endothelial cells and monocytes, especially during neoangiogenesis and embryogenesis (Gregory et al., 2014). Concerning the latter, the human placenta, especially syncytiotrophoblast is an important source of ENG (Gougos and Letarte, 1990). The primary roles of ENG include angiogenesis, endothelial cell differentiation and regulation of vascular tone through eNOS (Ahmad and Ahmed, 2004). Proteolytic cleavage of the extracellular domain of endoglin, generates sEng that presumably functions as limiting factor for the activity of TGF-β and the coupled eNOS (**Figure 3**; Qu et al., 1998; Bourdeau et al., 1999). Since TGF-β acts as anti-inflammatory and vasodilator growth factor, its elimination by sEng leads to endothelial dysfunction characterized by vasoconstriction, overexpression of adhesion molecules and reduced T cells characterizing preeclamptic women (Matsubara et al., 2000; Ahmed, 2011). By using experimental model of preeclampsia, it was shown that sEng and sFlt-1 act synergistically to induce endothelial dysfunction especially the severe variant of the disease, namely HELLP syndrome (Santner-Nanan et al., 2009). Similarly, circulating sEng was found to be high in preeclamptic women even prior to the disease manifestations correlating with disease severity and falls after delivery (Levine et al., 2004; Venkatesha et al., 2006), making it a reliable predictor of patients destined to develop severe early-onset preeclampsia (Robinson and Johnson, 2007). The regulators of sEng release are largely unknown, however like sFlt-1, it was reported that both cytokines (Zhou et al., 2010), and autoantibodies to angiotensin II AT-1 receptors stimulate (Cudmore et al., 2007) and heme oxygenase-1 (HO-1) inhibits its release (see later) (Zhou et al., 2010).

Other Vasoactive Substances

One of the major features of preeclampsia is generalized vasoconstriction and reduced plasma volume, assumedly due to endothelial activation even weeks before clear evidence of the disease (Roberts et al., 1989; Roberts and Lain, 2002). Endothelial dysfunction is characterized by reduced blood flow to virtually all organs in preeclamptic women due to vasoconstriction. The latter is partially attributed to imbalance in neurohormonal systems, including activation of the sympathetic nervous system and renin angiotensin aldosterone system (RAAS) as well as endothelin (ET-1) (Gant et al., 1973; Roberts and Lain, 2002). On the other hand, endothelium-dependent vasodilation (PGs, VEGF, TGF-β, and NO system) is also attenuated in preeclamptic patients (Fischer et al., 2000; Yoshida et al., 2000), secondary to oxidative stress which is known to provoke endothelial dysfunction (Roberts et al., 1989; McKinney et al., 2000). Partial restoration of the balance (even for a short while) by water immersion of preeclamptic women increased cardiac output and reduced systemic vascular resistance (SVR), yet to a lower extent than normal pregnant women (Elvan-Taspinar et al., 2006). Yet, the therapeutic potential for water immersion in preeclampsia appears to be limited (Elvan-Taspinar et al., 2006). Several studies have reported elevated ET-1 levels in preeclampsia and some of them demonstrated a positive correlation between ET-1 and the severity of symptoms (Taylor et al., 1990; Mastrogiannis et al., 1991; Benigni et al., 1992; Granger et al., 2006; George and Granger, 2011, 2012; George et al., 2012). The cadence of ET-1 as mediator of many preeclampsia manifestations is appealing in light of its potent vasoconstrictory, inflammatory and proteinuric properties (Davenport et al., 2016; Saleh et al., 2016; Bakrania et al., 2017). Support for this notion is derived from animal models of preeclampsia, where it has been shown that endothelin receptor blockers prevent the development of the disease (Saleh et al., 2016; Bakrania et al., 2017).

Finally, HO-1 plays an anti-inflammatory and inhibitory role on sFlt-1 and sEng release via its metabolite carbon monoxide (CO) (Ahmed, 2011). In line with HO-1 involvement in the pathogenesis of preeclampsia, women with the disease exhale less CO than women with normal pregnancies and HO-1 expression

decreases as the severity of preeclampsia increases (Ahmed, 2011). The downregulation of HO-1 aggravates the inflammatory aspect of preeclampsia, and deprives of the body from important anti stress and anti-oxidant defense mechanism (Ahmed, 2011).

Diagnosis of Preeclampsia

For more than half century, the clinical syndrome of preeclampsia is defined as *de novo* hypertension and new onset of proteinuria after mid pregnancy (ACOG practice bulletin, 2002). Hypertension is diagnosed when it is greater than 140 mmHg systolic or 90 mmHg diastolic at two separate times, more than 4 h apart in a woman after 20 weeks of gestation (Duley, 2003). In addition, proteinuria of >300 mg/day is milestone for the diagnosis of preeclampsia (Staff et al., 2013). However, in the last decade this concept has been challenged in light of the fact that the disease develops long time prior to its keen manifestations (Staff et al., 2013). Actually, early clinical signs of preeclampsia may be absent or unremarkable, and the reliability of these two hallmarks (hypertension and proteinuria) as gold standard is compromised, especially if the pregnant women suffer from predisposing conditions, such as chronic hypertension and CKD (Sibai and Stella, 2009). Therefore, the search for more sensitive and early biomarker of the disease continued all the time and is more zeal in the last decade. This issue is of great importance since early diagnosis of preeclampsia may be the first step in the journey for the development of effective treatment, especially if the biomarkers are of mechanistic relevance. In this context, new biomarkers were derived from the recent unprecedented advances in our understanding of the pathogenic mechanisms underlying preeclampsia (Ahmed, 2011; Staff et al., 2013; Phipps et al., 2016; Jim and Karumanchi, 2017). Specifically, it is now obvious that angiogenic imbalance, as reflected by elevated levels of sFlt-1, sEng, and ET-1 along decreased PlGF concentrations in the maternal circulation (Ahmed, 2011; Staff et al., 2013; Phipps et al., 2016; Saleh et al., 2016; Jim and Karumanchi, 2017), is the link between this syndrome and the malperfused placenta characterizing the early-onset pre-eclampsia, and the maternal genetic predisposition, as in the late-onset form. Therefore, sFlt-1, sEng, and PlGF are mounting biomarkers for the diagnosis of preeclampsia (Ahmed, 2011; Staff et al., 2013; Phipps et al., 2016; Jim and Karumanchi, 2017). Besides their diagnostic features, these biomarkers were found to possess prognostic features. For instance, Rana et al. (2013) showed that high ratio of sFlt to PlGF in preeclamptic women is associated with worse maternal and fetal outcomes compared with women with a lower ratio.

In a prospective multicenter observational study, Zeisler et al. (2016) examined whether ratio of serum sFlt-1 to PlGF predicts the absence or presence of preeclampsia in the short term in women with singleton pregnancies in whom preeclampsia was suspected (24 weeks 0 days to 36 weeks 6 days of gestation). These authors have shown that an sFlt-1-to-PlGF ratio of 38 or lower drawn at 24–37 weeks of gestation can reliably predict the absence of preeclampsia and fetal adverse outcomes within 1 week, with negative predictive values of 99.3 and 99.5%, respectively. Similarly, Sovio et al. (2017) who determined sFlt-1:PlGF ratio at 20, 28, and ≈36 weeks of gestational age in 4,099 women recruited to Pregnancy Outcome Prediction. At 28 gestational week, a sFlt-1:PlGF ratio >38 had a positive predictive value of 32% for preeclampsia and preterm birth. At 36 weeks, a sFlt-1:PlGF ratio >38 had a predictive value for severe preeclampsia of 20% in high-risk women and 6.4% in low-risk women. When sFlt-1:PlGF ratio was >110 it has predictive value of 30% for severe preeclampsia. Among low-risk women at 36 weeks, a sFlt-1:PlGF ratio ≤38 had a negative predictive value for severe preeclampsia of 99.2%. Collectively, the sFlt-1:PlGF ratio provided clinically useful prediction of the risk of the most important manifestations of preeclampsia, confirming the pioneer findings by Levine et al. (2004) and providing rational for the use of angiogenic biomarkers to stratify women at high risk for preeclampsia.

In similarity with sFlt-1, serum concentrations of sEng are elevated in preeclamptic women (Chen, 2009), as compared with stable levels throughout normal pregnancy. A positive correlation between the elevated serum levels of sEng and the severity of pre-eclampsia has been demonstrated (Chen, 2009). Noteworthy, serum sEng have been shown to be significantly increased before the onset of disease. Specifically, sEng levels increased as early as 9–11 weeks in pregnant women at risk for preeclampsia and by12–14 weeks in women with term preeclampsia (Levine et al., 2004). Thus, sEng could be used to predict preeclampsia at 11–13 week gestation (Akolekar et al., 2011) with precaution since high levels of sEng are detected also in other gestational disorders such as small gestational age, thus limiting its specificity. Therefore, the pattern of changes in the ratio of different combinations of PlGF/sEng; sflt-1 + sEng)/PlGF, at 13 weeks and around 20 weeks, is more informative than the individual biomarkers at single time-point screening (Levine et al., 2004; Romero et al., 2008; Rana et al., 2013).

Kidney Placenta Crosstalk

The kidney in normal pregnancy

There is an important crosstalk between the placenta and the kidney during normal pregnancy, as evident by adaptive anatomic and physiologic renal changes. The latter include an increase in renal size by 30% and length by 1–1.5 cm mainly due to the increased renal blood flow (RBF) as early as the first 4 weeks of pregnancy (Hussein and Lafayette, 2014). The collecting systems of both kidneys are normally dilated and are more pronounced on the right, therefore "Physiological hydronephrosis" can occur in late pregnancy. Moreover, reduction in BP secondary to generalized peripheral vasodilation due to the reduced SVR, is probably due to the increased resistance to angiotensin II (Gant et al., 1973). Likewise, imbalance between the vasodilatory prostacyclin and relaxin and vasoconstrictive thromboxane in favor of the first, and activation of nitric oxide (NO), a potent vasodilator that mediates endothelium dependent relaxation (Hussein and Lafayette, 2014), may contribute to this phenomenon. At the renal level, there is an increase in glomerular filtration rate (GFR) secondary to increased RBF by ~35–50% (Hussein and Lafayette, 2014). For this reason, normal pregnancy is accompanied by low serum creatinine, urea, sodium, uric acid levels and increased urinary protein excretion up to 300 mg/d (Hussein and Lafayette, 2014). The renal vasodilation is responsible also for the activation of the

RAAS. In fact, despite the elevated levels of renin and aldosterone in pregnant woman, both the BP and SVR are reduced (Gant et al., 1973).

The kidney in preeclampsia

The above-mentioned changes are partially realized in complicated pregnancy such as preeclampsia, where pathologic changes in both the placenta and the kidneys take place. One of the most vulnerable organ to miss adaptive changes during preeclampsia is the kidney, where glomerular endotheliosis and proteinuria develop (Spargo et al., 1959; Gartner et al., 1998; Craici et al., 2013). The hallmark characteristic renal pathologic lesion of preeclampsia "glomerular endotheliosis" is characterized by an enlarged bloodless glomerulus with obliteration of the capillary lumen, but usually not accompanied by prominent capillary thrombi (**Figure 4**; Spargo et al., 1959; Hussein and Lafayette, 2014). Initially, endothelial cell swelling and disruption of their fenestrae were thought to be the cause of proteinuria seen in preeclampsia (Hussein and Lafayette, 2014). However, there is increasing evidence that damage to the podocytes, the visceral epithelial glomerular cell, is largely responsible for the proteinuria (**Figure 4**). In this context podocyturia (loss of podocytes in the urine), along shedding of slit diaphragm proteins such as nephrin, podocin, synaptopodin and podocalyxin were noticed in preeclampsia, and even precede the typical clinical features of preeclampsia by several weeks (Garovic et al., 2007a,b, 2013; Aita et al., 2009; Zhao et al., 2009, 2011; Facca et al., 2012; Jim et al., 2012; Kelder et al., 2012; Wang et al., 2012; Chen et al., 2013; Son et al., 2013). It should be emphasized that these slit diaphragm proteins play a key role in maintaining the integrity of the glomerular barrier (Kestila et al., 1998).

The end result of this disruption of the glomerular filtration barrier and podocyte detachment is proteinuria (**Figure 4**; Spargo et al., 1959; Craici et al., 2013). In fact, there is a positive correlation between the grade of podocyturia and the severity of proteinuria. One of the main mediators of the adverse renal consequences of preeclampsia is ET-1 (Taylor et al., 1990; Mastrogiannis et al., 1991; Benigni et al., 1992; Granger et al., 2006; George and Granger, 2011, 2012; George et al., 2012; Verdonk et al., 2015; Davenport et al., 2016; Saleh et al., 2016; Bakrania et al., 2017). Support for this notion is derived from the observation that pre-eclamptic sera are not directly toxic to cultured podocytes, but if the glomerular capillary endothelium is exposed to sera from pre-eclamptic women it produces podocytes damage via ETA receptor subtype (Collino et al., 2008). Addition keen evidence for the involvement of ET-1 system in the pathogenesis of renal dysfunction characterizing preeclampsia came from the observation that podocyte damage and shedding can be prevented by ETA blockers (George and Granger, 2011; Verdonk et al., 2015; Bakrania et al., 2017). However, in the last decade, there is growing evidence that imbalance between the proangiogenic and anti angiogenic factors plays a key role in podocyte injury (Genbacev et al., 1997; Fulton et al., 1999; Robertson et al., 2003; Venkatesha et al., 2006; Baelde et al., 2007; Sison et al., 2010; Bertuccio et al., 2011; Veron et al., 2012). This concept is supported by the observation that bevacizumab, an anti-VEGF antibody used to treat patients with various types of cancer or diabetic proliferative retinopathy causes hypertension and proteinuria mimicking the effect of sFlt-1 (Eremina et al., 2008; Muller-Deile and Schiffer, 2011; Hayman et al., 2014). Interestingly, the renal findings in patients who were treated with bevacizumab including endotheliosis, thrombotic microangiopathy, and podocytes shedding, are similar to those found in preeclamptic state (Eremina et al., 2008; Muller-Deile and Schiffer, 2011; Hayman et al., 2014). Kidney damage during preeclampsia as evident by endothelial and podocytes' loss contributes to the increased risk of later hypertension, CKD, ischemic heart disease, stroke, persistent proteinuria and finally ends stage renal disease (ESRD) (LaMarca B.D. et al., 2008; Vikse et al., 2008, 2012; McDonald et al., 2010; Kattah et al., 2013; Wang et al., 2013).

As mentioned above, superficial placental implantation due to abnormal angiogenesis is the early driving event for the development of preeclampsia. The imbalance between the pro-angiogenic VEGF and PlGF, and the antiangiogenic sFlt-1 and sEng plays a central role in the pathogenesis of placental hypoxia, as both VEGF and PlGF are essential for fetal and placental angiogenesiss (Lam et al., 2005; Sison et al., 2010; Bertuccio et al., 2011; Powe et al., 2011; Rana et al., 2012; Veron et al., 2012). Excessive production of antiangiogenic sFlt-1 and sEng reduces the bioavailability of free pro-angiogenic PlGF and VEGF, by binding and neutralizes VEGF and PlGF, thus reducing the availability of free VEGF for fetal and placental angiogenesis. In comparison, the sEng is implicated in neutralizing TGF-β, an anti-inflammatory growth factor (Roberts et al., 1989) that activates eNOS (Phipps et al., 2016). This imbalance leads to systemic endothelial dysfunction, including in the kidney (Kaufmann et al., 2003; Venkatesha et al., 2006), where disruption of slit diaphragm was reported (Garovic et al., 2007a; Henao et al., 2008; Zhao et al., 2009), as VEGF is essential for the maintenance glomerular barrier (Baelde et al., 2007). Support for the adverse effect of preeclampsia on glomerular barrier was reported by Henao et al. (2008). These authors demonstrated that when a human podocyte cell line was stimulated with serum from women with preeclampsia, disruption of CD2AP, podocin and actin were observed, but not when sera from normal pregnancy was added. Furthermore, the mean resistance value of podocytes cultured with serum from women with preeclampsia was significantly lower than podocytes cultured with serum from controls. This effect is mediated by ET-1 release by endothelial glomerular cells as preeclamptic sera induce nephrin shedding from podocytes (Romero et al., 2008). In this context, Elevated levels of ET-1, autoantibodies to the angiotensin II type I receptor, tumor necrosis factor α (TNFα) and interleukin-6 (IL-6) are also elevated in pre-eclampsia (Taylor et al., 1990; Mastrogiannis et al., 1991; Benigni et al., 1992; Granger et al., 2006; LaMarca B. et al., 2008; LaMarca B.D. et al., 2008; George and Granger, 2011, 2012; George et al., 2012).

Preeclampsia is commonly (but not always) accompanied by new onset proteinuria (>300 mg/d) or worsening proteinuria diagnosed after 20 weeks of pregnancy and generalized edema. The latter is mainly due to primary renal retention of salt and water despite the suppression of RAAS during preeclampsia due

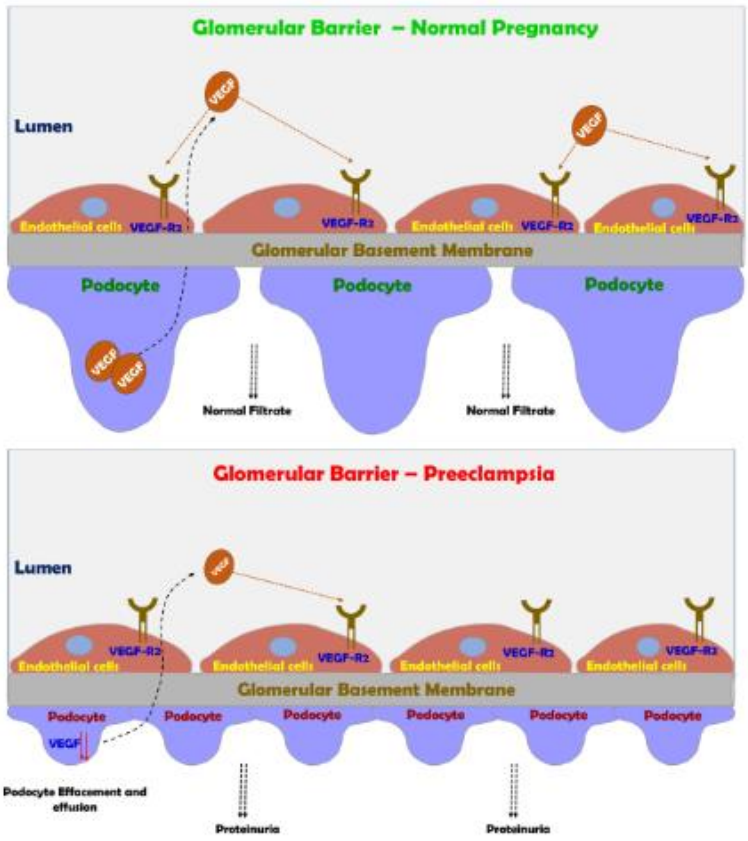

FIGURE 4 | Preeclampsia-induced renal dysfunction. Under normal condition, VEGF plays a central role in maintaining the integrity of glomerular barrier as evident by healthy podocytes with normal foot process and slit diaphragm proteins. Under preeclamptic condition, angiogenic imbalance develops mainly due to sFlt-1 and sEng, leading to podocyte and endothelial damage in the glomerular filtration barrier and subsequently to the development of proteinuria.

to vasoconstriction, in contrast to its upregulation in normal pregnancy, which is characterized by vasodilation (Schrier, 1988). Thus, the edema-accompanied preeclampsia resembles the "overfill" edematous clinical settings. Another abnormal laboratory tests include elevated levels of creatinine, urea, uric acid levels along hypocalciuria, decreased urate excretion, and proteinuria.

Novel Mechanisms Based Therapeutics

Despite the rapid progress in understanding the mechanisms underlying the pathogenesis of preeclampsia, the treatment options remained very limited, except for early delivery. The current treatment options such as low Na^+ diet, diuretics, Ca^{++} supplementation, Vitamin C and E were ineffective in most cases (Jim and Karumanchi, 2017). Aspirin moderately reduced the incidence of preterm preeclampsia in high-risk patients when given the drug at 11–14 weeks of gestation until 36 weeks (Rolnik et al., 2017). Therefore, there is unmet need for novel therapies to treat preeclampsia. Fortunately, as a token for unraveling the role of soluble vascular factors in preeclampsia, several new therapeutics have been developed that

target implicated circulating angiogenic factors, including sFlt-1 (**Figure 5**; Sircar et al., 2015; Jim and Karumanchi, 2017). Specifically, these strategies rely on correcting the angiogenic balance, either by promoting proangiogenic factors or by blocking those of antiangiogenic properties. As outlined above, sFlt 1 is involved in the hemodynamic and pathophysiologic changes characterizing preeclampsia such as hypertension, renal dysfunction and shallow placentation (as the case in early-onset preeclampsia). Thus, elimination or reduction of the circulating levels of this deleterious anti-angiogenic factor below critical levels is supposed to ameliorate the angiogenic imbalance. Restoring angiogenic balance eventually improves the clinical signs of preeclampsia as has been confirmed in clinical and experimental models of the disease (Bergmann et al., 2010). In line with this assumption, an early study in five women with severe, early onset preeclampsia has demonstrated that negatively charged dextran sulfate cellulose column apheresis significantly decreased the plasma levels of sFlt-1 and attenuate the deleterious manifestations of the disease, including BP and proteinuria (Thadhani et al., 2011). Interestingly, pregnancy was prolonged by 15–23 days in these women without substantial side effects on the mother or fetus. In agreement with these results, a recent study has demonstrated that sFlt-1 removal by more efficient extracorporeal removal approach in 11 women who suffered from severe, early preeclampsia reduced proteinuria and prolonged pregnancy by 2–21 days depending on the number of courses underwent by the women, without causing major adverse maternal or fetal consequences (**Figure 5**; Thadhani et al., 2016). Additional approach for the reduction of sFlt-1 applied proton pump inhibitors (PPIs) in experimental model of the disease, namely placental sFlt-1 transgenic mice and *in vitro* human primary placental tissue and HUVEC (Onda et al., 2017). Proton pump inhibitors (PPIs) decrease sFlt-1 and sEng secretion, attenuate endothelial dysfunction, dilate blood vessels, decrease BP, and exert antioxidant and anti-inflammatory effects. The authors concluded that PPIs have therapeutic potential for preeclampsia and other diseases characterized by endothelial dysfunction (Onda et al., 2017). At the clinical level, PPI used by pregnant women (430 in number) was associated with decrease in sFlt-1 (Saleh et al., 2017). Moreover, their plasma endoglin and ET-1 levels were lower while sFlt-1 levels correlated positively with both. These findings suggest that PPI may bear therapeutic potential for preeclampsia, although prospective trials are still warranted.

In agreement with their physiological role, replenishing the circulatory levels of VEGF or PlGF exerted beneficial effects in experimental preeclampsia. Specifically, recombinant human PlGF supplementation restores the imbalance and abolished hypertension and GFR impairment in a rat preeclampsia model induced by reduced uterine perfusion pressure (RUPP) (Spradley et al., 2016). Since 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) have been shown to ameliorate the signs of experimental preeclampsia via upregulation of PlGF expression (Kumasawa et al., 2011), their efficacy and

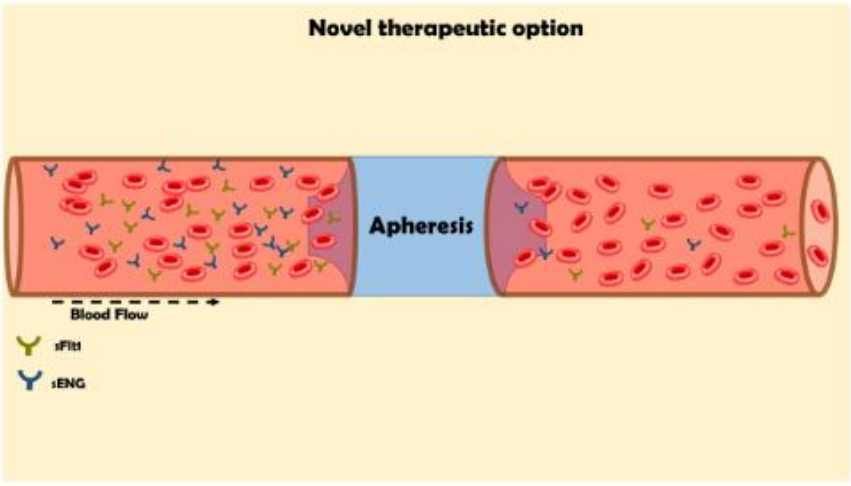

FIGURE 5 | Innovative approach for the elimination of the elevated levels of sFlt-1 by apheresis for the management of preeclampsia. The maternal blood flow through columns, which contains antibodies against sFlt1 in order to remove it from the circulation.

safety for prevention of preeclampsia are currently being tested in two clinical trials (Ahmed, 2011; Costantine and Cleary, 2013). Additional alternative to these approaches is administration of VEGF 121, which was shown to alleviate symptoms of preeclampsia including hypertension and renal injury (proteinuria, glomerular endotheliosis) in experimental model of the disease (Li et al., 2007). Co-administration of adenovirus and VEGF in an sFlt-1-induced model of preeclampsia rescued endothelial dysfunction along reduction of free circulatory sFlt-1 by ~70% (Bergmann et al., 2010). Similarly, chronic infusion of VEGF121 via osmotic minipumps during late gestation reduced sFlt-1, restores GFR and endothelial function, and reduces high BP in experimental model of placental ischemia (Li et al., 2007). Interestingly, in all the above-mentioned studies administration of VEGF to sFlt-1 transgenic animals caused reduction of sFlt-1 along improvement of endothelial function (Bergmann et al., 2010). Although these results suggest that VEGF121 may be a candidate molecule for management of preeclampsia and its related complications, it should be emphasized that such approach may increase the fetal weight as the case in diabetic women, and may cause undesirable side effects such as edema due to its unselective binding to both VEGFR-1 and VEGFR-2.

Although, experimental studies in animal models of preeclampsia have shown that endothelin receptor blockers prevent the development of the disease (Saleh et al., 2016; Bakrania et al., 2017), clinical trials are still needed to validate these promising findings. Moreover, it should be emphasized that rebalancing the angiogenic ratios will improve the peripheral manifestations of the syndrome, but do not impact the underlying pathology of the early-onset cases, such as the acute atherotic changes in the spiral arteries. Hence, there a is danger of increasing stillbirths through prolonging a pregnancy in which uteroplacental perfusion is impaired.

SUMMARY

Preeclampsia is a multifactorial clinical state that adversely affects almost all vital organs of pregnant women. After a half century of stumbling in understanding the molecular basis of the disease, the last decade has witnessed great advancement in the research of preeclampsia as evident by the discovery of wide battery of novel biomarkers that allow early diagnosis of the disease and prediction of the outcome.

In early-onset, pre-eclampsia there is clear evidence of reduced maternal spiral artery conversion in early pregnancy due to deficient trophoblast invasion and arterial remodeling, resulting in aberrant maternal-fetal interactions during early pregnancy and placental malperfusion. Oxidative stress of the placenta causes the increased secretion of sFLT-1 and reduced PlGF, and so explains the biomarker patterns. The abnormal angiogenic ratios are subsequent to the impaired placentation, and not the cause of it, as there is no evidence that sFLT affects trophoblast invasion. In contrast, in late-onset pre-eclampsia there is slight reduction in arterial conversion and the placental perfusion is maintained or even increased. Therefore, there is only minimal placental stress and sFLT and PLGF secretion by the placenta are close to normal range. These cases, which represent the overwhelming majority of pre-eclampsia, are now thought to be due to a genetic maternal pre-disposition to cardiovascular disease, which manifests as pre-eclampsia in response to pregnancy-induced stress.

Thus, sFlt-1 and sEng do not serve solely as biomarkers, rather they are responsible for the angiogenic imbalance and generalized endothelial dysfunction characterizing preeclampsia. The new insights into the pathogenesis of this clinical condition will provide great opportunity to improve the care of preeclamptic women before delivery and undoubtedly will lead 1 day to the development of novel strategies for prevention and treatment of the disease. Pipeline clinical trials based on elimination of serum sFlt-1 by means of apheresis yielded promising results indicating that the remedy for this prevalent dangerous entity is within reach (Nakakita et al., 2015; Easterling, 2016).

AUTHOR CONTRIBUTIONS

ZA writing the section that deals with the renal aspect of preeclampsia and organizing all sections. JJ writing the introduction and organizing the MS. AJ writing the biochemical biomarkers of preeclampsia. ZAA writing the vascular aspects of preeclampsia and the molecular base underlying the pathogenesis of the diseases, editing the whole MS.

ACKNOWLEDGMENTS

The authors are grateful for Safa Kinaneh, M.Sc. for her technical assistance.

REFERENCES

ACOG practice bulletin (2002). Diagnosis and management of preeclampsia and eclampsia. Number 33, January. American College of Obstetricians and Gynecologists. *Int. J. Gynaecol. Obstet.* 77, 67–75.

Ahmad, S., and Ahmed, A. (2004). Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. *Circ. Res.* 95, 884–891. doi: 10.1161/01.RES.0000147365.86159.f5

Ahmad, S., Hewett, P. W., Wang, P., Al-Ani, B., Cudmore, M., Fujisawa, T., et al. (2006). Direct evidence for endothelial vascular endothelial growth factor receptor-1 function in nitric oxide-mediated angiogenesis. *Circ. Res.* 99, 715–722. doi: 10.1161/01.RES.0000243989.46006.b9

Ahmed, A. (1997). Heparin-binding angiogenic growth factors in pregnancy: a review. *Placenta* 18, 215–258. doi: 10.1016/S0143-4004(97)80091-4

Ahmed, A. (2011). New insights into the etiology of preeclampsia: identification of key elusive factors for the vascular complications. *Thromb. Res.* 127(Suppl. 3), S72–S75. doi: 10.1016/S0049-3848(11)70020-2

Aita, K., Etoh, M., Hamada, H., Yokoyama, C., Takahashi, A., Suzuki, T., et al. (2009). Acute and transient podocyte loss and proteinuria in preeclampsia. *Nephron Clin. Pract.* 112, c65–c70. doi: 10.1159/000213083

Akolekar, R., Syngelaki, A., Sarquis, R., Zvanca, M., and Nicolaides, K. H. (2011). Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. *Prenat. Diagn.* 31, 852–852. doi: 10.1002/pd.2828

Al-Jameil, N., Aziz Khan, F., Fareed Khan, M., and Tabassum, H. (2014). A brief overview of preeclampsia. *J. Clin. Med. Res.* 6, 1–7.

Backes, C. H., Markham, K., Moorehead, P., Cordero, L., Nankervis, C. A., and Giannone, P. J. (2011). Maternal preeclampsia and neonatal outcomes. *J. Pregnancy* 2011:214365. doi: 10.1155/2011/214365

Baelde, H. J., Eikmans, M., Lappin, D. W. P., Doran, P. P., Hohenadel, D., Brinkkoetter, P. T., et al. (2007). Reduction of VEGF-A and CTGF expression in diabetic nephropathy is associated with podocyte loss. *Kidney Int.* 71, 637–645. doi: 10.1038/sj.ki.5002101

Bakrania, B., Duncan, J., Warrington, J. P., and Granger, J. P. (2017). The endothelin type a receptor as a potential therapeutic target in preeclampsia. *Int. J. Mol. Sci.* 18:E522. doi: 10.3390/ijms18030522

Baltajian, K., Bajracharya, S., Salahuddin, S., Berg, A. H., Geahchan, C., Wenger, J. B., et al. (2016). Sequential plasma angiogenic factors levels in women with suspected preeclampsia. *Am. J. Obstet. Gynecol.* 215, 89.e1–89.e10. doi: 10.1016/j.ajog.2016.01.168

Benigni, A., Orisio, S., Gaspari, P., Frusca, T., Amuso, G., and Remuzzi, G. (1992). Evidence against a pathogenetic role for endothelin in pre-eclampsia. *Br. J. Obstet. Gynaecol.* 99, 798–802. doi: 10.1111/j.1471-0528.1992.tb14409.x

Berg, C. J., Atrash, H. K., Koonin, L. M., Tucker M. (1996). Pregnancy-related mortality in the United States, 1987-1990. *Obstet. Gynecol.* 88, 161–167. doi: 10.1016/0029-7844(96)00135-4

Bergmann, A., Ahmad, S., Cudmore, M., Gruber, A. D., Wittschen, P., Lindenmaier, W., et al. (2010). Reduction of circulating soluble Flt-1 alleviates preeclampsia-like symptoms in a mouse model. *J. Cell Mol. Med.* 14, 1857–1867. doi: 10.1111/j.1582-4934.2009.00820.x

Bertuccio, C., Veron, D., Aggarwal, P. K., Holzman, L., and Tufro, A. (2011). Vascular endothelial growth factor receptor 2 direct interaction with nephrin links VEGF-A signals to actin in kidney podocytes. *J. Biol. Chem.* 286, 39933–39944. doi: 10.1074/jbc.M111.241620

Bourdeau, A., Dumont, D. J., and Letarte, M. (1999). A murine model of hereditary hemorrhagic telangiectasia. *J. Clin. Invest.* 104, 1343–1351. doi: 10.1172/JCI8088

Brosens, I. A., Robertson, W. B., and Dixon, H. G. (1972). The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet. Gynecol. Annu.* 1, 177–191.

Burke, S. D., Zsengeller, Z. K., Khankin, E. V., Lo, A. S., Rajakumar, A., DuPont, J. J., et al. (2016). Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia. *J. Clin. Invest.* 126, 2561–2574. doi: 10.1172/JCI83918

Burton, G. J., Woods, A. W., Jauniaux, E., and Kingdom, J. C. (2009). Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta* 30, 473–482. doi: 10.1016/j.placenta.2009.02.009

Chen, G., Zhang, L., Jin, X., Zhou, Y., Niu, J., Chen, J., et al. (2013). Effects of angiogenic factors, antagonists, and podocyte injury on development of proteinuria in preeclampsia. *Reprod. Sci.* 20, 579–588. doi: 10.1177/1933719112459227

Chen, Y. (2009). Novel angiogenic factors for predicting preeclampsia: sFlt-1, PlGF, and soluble endoglin. *Open Clin. Chem. J.* 2, 1–6. doi: 10.2174/1874241600902010001

Cindrova-Davies, T. (2009). Gabor than award lecture 2008: pre-eclampsia - from placental oxidative stress to maternal endothelial dysfunction. *Placenta* 30(Suppl. A), S55–S65. doi: 10.1016/j.placenta.2008.11.020

Cindrova-Davies, T., Sanders, D. A., Burton, G. J., and Charnock-Jones D S. (2011). Soluble FLT1 sensitizes endothelial cells to inflammatory cytokines by antagonizing VEGF receptor-mediated signalling. *Cardiovasc. Res.* 89, 671–679. doi: 10.1093/cvr/cvq346

Clowse, M. E. B., Jamison, M., Myers, E., and James A H. (2008). A national study of the complications of lupus in pregnancy. *Am. J. Obstet. Gynecol.* 199, 127.e1–127.e6. doi: 10.1016/j.ajog.2008.03.012

Collino, F., Bussolati, B., Gerbaudo, E., Marozio, L., Pelissetto, S., Benedetto, C., et al. (2008). Preeclamptic sera induce nephrin shedding from podocytes through endothelin-1 release by endothelial glomerular cells. *Am. J. Physiol. Renal Physiol.* 294, F1185–F1194. doi: 10.1152/ajprenal.00442.2007

Conrod, D. V., Hickok, D. E., Zhu, K., Easterling, T. R., and Daling, J. R. (1995). Risk factors for preeclampsia in twin pregnancies: a population-based cohort study. *Obstet. Gynecol.* 85(5 Pt 1):645–650. doi: 10.1016/0029-7844(95)00049-W

Costantino, M. M., and Cleary, K. (2013). Pravastatin for the prevention of preeclampsia in high-risk pregnant women. *Obstet. Gynecol.* 121(2 Pt 1), 349–353. doi: 10.1097/AOG.0b013e31827d8ad5

Craici, I. M., Wagner, S. J., Bailey, K. R., Fitz-Gibbon, P. D., Wood-Wentz, C. M., Turner, S. T., et al. (2013). Podocyturia predates proteinuria and clinical features of preeclampsia: longitudinal prospective study. *Hypertension* 61, 1289–1296. doi: 10.1161/HYPERTENSIONAHA.113.01115

Cudmore, M., Ahmad, S., Al-Ani, B., Fujisawa, T., Coxall, H., Chudasama, K., et al. (2007). Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. *Circulation* 115, 1789–1797. doi: 10.1161/CIRCULATIONAHA.106.660134

Davenport, A. P., Hyndman, K. A., Dhaun, N., Southan, C., Kohan, D. E., Pollock, J. S., et al. (2016). Endothelin. *Pharmacol. Rev.* 68, 357–418. doi: 10.1124/pr.115.011833

De Falco, S. (2012). The discovery of placenta growth factor and its biological activity. *Exp. Mol. Med.* 44, 1–9. doi: 10.3858/emm.2012.44.1.025

Duley, L. (2003). Pre-eclampsia and the hypertensive disorders of pregnancy. *Br. Med. Bull.* 67, 161–176. doi: 10.1093/bmb/ldg005

Easterling, T. R. (2016). Apheresis to treat preeclampsia: insights, opportunities and challenges. *J. Am. Soc. Nephrol.* 27, 663–665. doi: 10.1681/ASN.2015070794

Elvan-Taspinar, A., Franx, A., Delprat, C. C., Bruinse, H. W., and Koomans, H. A. (2006). Water immersion in preeclampsia. *Am. J. Obstet. Gynecol.* 195, 1590–1595. doi: 10.1016/j.ajog.2006.05.007

Eremina, V., Jefferson, J. A., Kowalewska, J., Hochster, H., Haas, M., Weisstuch, J., et al. (2008). VEGF inhibition and renal thrombotic microangiopathy. *N. Engl. J. Med.* 358, 1129–1136. doi: 10.1056/NEJMoa0707330

Pacca, T. A., Kirsztajn, G. M., Pereira, A. B., Moreira, S. R., Teixeira, V. P., Nishida, S. K., et al. (2012). Renal evaluation in women with preeclampsia. *Nephron Extra* 2, 125–132. doi: 10.1159/000338271

Perrara, N. (2004). Vascular endothelial growth factor: basic science and clinical progress. *Endocr. Rev.* 25, 581–611. doi: 10.1210/er.2003-0027

Fischer, T., Schnaidter, M. P., Schobel, H. P., Heusser, K., Langenfeld, M., and Schmieder R. E. (2000). Vascular reactivity in patients with preeclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. *Am. J. Obstet. Gynecol.* 183, 1489–1494. doi: 10.1067/mob.2000.107323

Fulton, D., Gratton, J. P., McCabe, T. J., Fontana, J., Fujio, Y., Walsh, K., et al. (1999). Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature* 399, 597–601. doi: 10.1038/21218

Gant, N. F., Daley, G. L., Chand, S., Whalley, P. J., and MacDonald, P. C. (1973). A study of angiotensin II pressor response throughout primigravid pregnancy. *J. Clin. Invest.* 52, 2682–2689. doi: 10.1172/JCI107462

Garovic, V. D., Craici, I. M., Wagner, S. J., White, W. M., Brost, B. C., Rose, C. H., et al. (2013). Mass spectrometry as a novel method for detection of podocyturia in pre-eclampsia. *Nephrol. Dial. Transplant.* 28, 1555–1561. doi: 10.1093/ndt/gfs074

Garovic, V. D., Wagner, S. J., Petrovic, L. M., Gray, C. E., Hall, P., Sugimoto, H., et al. (2007a). Glomerular expression of nephrin and synaptopodin, but not podocin, is decreased in kidney sections from women with preeclampsia. *Nephrol. Dial. Transplant.* 22, 1136–1143. doi: 10.1093/ndt/gfl711

Garovic, V. D., Wagner, S. J., Turner, S. T., Rosenthal, D. W., Watson, W. J., Brost, B. C., et al. (2007b). Urinary podocyte excretion as a marker for preeclampsia. *Am. J. Obstet. Gynecol.* 196, 320.e1–320.e7. doi: 10.1016/j.ajog.2007.02.007

Gartner, H. V., Sammoun, A., Wehrmann, M., Grossmann, T., Junghans, R., and Weißing, C. (1998). Preeclamptic nephropathy – an endothelial lesion. A morphological study with a review of the literature. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 77, 11–27. doi: 10.1016/S0301-2115(97)00219-4

Genbacev, O., Zhou, Y., Ludlow, J. W., and Fisher, S. J. (1997). Regulation of human placental development by oxygen tension. *Science* 277, 1669–1672. doi: 10.1126/science.277.5332.1669

George, E. M., and Granger, J. P. (2010). Recent insights into the pathophysiology of preeclampsia. *Expert Rev. Obstet. Gynecol.* 5, 557–566. doi: 10.1586/eog.10.45

George, E. M., and Granger, J. P. (2011). Endothelin: key mediator of hypertension in preeclampsia. *Am. J. Hypertens.* 24, 964–969. doi: 10.1038/ajh.2011.99

George, E. M., and Granger, J. P. (2012). Linking placental ischemia and hypertension in preeclampsia: role of endothelin 1. *Hypertension* 60, 507–511. doi: 10.1161/HYPERTENSIONAHA.112.194845

George, E. M., Palei, A. C., and Granger, J. P. (2012). Endothelin as a final common pathway in the pathophysiology of preeclampsia: therapeutic

implications. *Curr. Opin. Nephrol. Hypertens.* 21, 157–162. doi: 10.1097/MNH.0b013e32835004b

Geusens, N., Verlohren, S., Luyten, C., Taube, M., Hering, L., Vercruysse, L., et al. (2008). Endovascular trophoblast invasion, spiral artery remodelling and uteroplacental haemodynamics in a transgenic rat model of pre-eclampsia. *Placenta* 29, 614–623. doi: 10.1016/j.placenta.2008.04.005

Ghulmiyyah, L., and Sibai, B. (2012). Maternal mortality from preeclampsia/eclampsia. *Semin. Perinatol.* 36, 56–59. doi: 10.1053/j.semperi.2011.09.011

Gerogos, A., and Letarte, M. (1990). Primary structure of endoglin, an RGD-containing glycoprotein of human endothelial cells. *J. Biol. Chem.* 265, 8361–8364.

Granger, J. P., Abram, S., Stec, D., Chandler, D., Speed, J., and LaMarca, B. (2006). Endothelin, the kidney, and hypertension. *Curr. Hypertens. Rep.* 8, 298–303. doi: 10.1007/s11906-006-0068-x

Gregory, A. L., Xu, G., Sotov, V., and Letarte, M. (2014). Review: the enigmatic role of endoglin in the placenta. *Placenta* 35, 593–599. doi: 10.1016/j.placenta.2013.10.020

Hayman, S. R., Calle, J. C., Jatoi, A., Craici, I. M., Wagner, S. J., Weaver, A. L., et al. (2014). Urinary podocyte excretion and proteinuria in patients treated with antivascular endothelial growth factor therapy for solid tumor malignancies. *Oncology* 86, 271–278. doi: 10.1159/000360180

Henao, D. E., Arias, L. P., Mathieson, P. W., Ni, L., Walsh, G. I., Bueno, J. C., et al. (2008). Preeclamptic sera directly induce slit-diaphragm protein redistribution and alter podocyte barrier-forming capacity. *Nephron Exp. Nephrol.* 110, e73–e81. doi: 10.1159/000166993

Hussein, W., and Lafayette, R. A. (2014). Renal function in normal and disordered pregnancy. *Curr. Opin. Nephrol. Hypertens.* 23, 46–53. doi: 10.1097/01.mnh.0000436545.94132.52

Iwasaki, H., Kawamoto, A., Tjwa, M., Horii, M., Hayashi, S., Oyamada, A., et al. (2011). PlGF repairs myocardial ischemia through mechanisms of angiogenesis, cardioprotection and recruitment of myo-angiogenic competent marrow progenitors. *PLoS One* 6:e24872. doi: 10.1371/journal.pone.0024872

Jim, B., Jean-Louis, P., Qipo, A., Garry, D. Mian, S., and Matos, T. (2012). Podocyturia as a diagnostic marker for preeclampsia amongst high-risk pregnant patients. *J. Pregnancy* 2012:984630. doi: 10.1155/2012/984630

Jim, B., and Karumanchi, S. A. (2017). Preeclampsia: pathogenesis, prevention, and long-term complications. *Semin. Nephrol.* 37, 386–397. doi: 10.1016/j.semnephrol.2017.05.011

Kabbinavar, F., Hurwitz, H. I., Fehrenbacher, L., Meropol, N. J., Novotny, W. F., Lieberman, G., et al. (2003). Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 21, 60–65. doi: 10.1200/JCO.2003.10.066

Kanasaki, K., Palmsten, K., Sugimoto, H., Ahmad, S., Hamano, Y., Xie, L., et al. (2008). Deficiency in catechol-O-methyltransferase and 2-methoxyoestradiol is associated with pre-eclampsia. *Nature* 453, 1117–1121. doi: 10.1038/nature06951

Kar, M. (2014). Role of biomarkers in early detection of preeclampsia. *J. Clin. Diagn. Res.* 8, BE01–BE04. doi: 10.7860/JCDR/2014/7969.4261

Kattah, A. G., Asad, R., Scantlebury, D. C., Bailey, K. R., Wiste, H. J., Hunt, S. C., et al. (2013). Hypertension in pregnancy is a risk factor for microalbuminuria later in life. *J. Clin. Hypertens.* 15, 617–625. doi: 10.1111/jch.12116

Kaufmann, P., Black, S., and Huppertz, B. (2003). Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol. Reprod.* 69, 1–7. doi: 10.1095/biolreprod.102.014977

Kelder, T. P., Penning, M. E., Uh, H. W., Cohen, D., Bloemenkamp, K. W. M., Bruijn, J. A., et al. (2012). Quantitative polymerase chain reaction-based analysis of podocyturia is a feasible diagnostic tool in preeclampsia. *Hypertension* 60, 1538–1544. doi: 10.1161/HYPERTENSIONAHA.112.201681

Kendall, R. L., and Thomas, K. A. (1993). Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. *Proc. Natl. Acad. Sci. U.S.A.* 90, 10705–10709. doi: 10.1073/pnas.90.22.10705

Kestila, M., Lenkkeri, U., Mannikko, M., Lamerdin, J., McCready, P., Putaala, H., et al. (1998). Positionally cloned gene for a novel glomerular protein - nephrin - is mutated in congenital nephrotic syndrome. *Mol. Cell* 1, 575–582. doi: 10.1016/S1097-2765(00)80057-X

Kumasawa, K., Ikawa, M., Kidoya, H., Hasuwa, H., Saito-Fujita, T., Morioka, Y., et al. (2011). Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. *Proc. Natl. Acad. Sci. U.S.A.* 108, 1451–1455. doi: 10.1073/pnas.1011293108

Lam, C., Lim, K. H., and Karumanchi, S. A. (2005). Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia. *Hypertension* 46, 1077–1085. doi: 10.1161/01.HYP.0000187899.34579.b0

LaMarca, B., Wallukat, G., Llinas, M., Herse, F., Dechend, R., and Granger, J. P. (2008). Autoantibodies to the angiotensin type I receptor in response to placental ischemia and tumor necrosis factor alpha in pregnant rats. *Hypertension* 52, 1168–1172. doi: 10.1161/HYPERTENSIONAHA.108.120576

LaMarca, B. D., Gilbert, J., and Granger, J. P. (2008). Recent progress toward the understanding of the pathophysiology of hypertension during preeclampsia. *Hypertension* 51, 982–988. doi: 10.1161/HYPERTENSIONAHA.107.108837

Levine, R. J., Maynard, S. E., Qian, C., Lim, K. H., England, L. J., Yu, K. F., et al. (2004). Circulating angiogenic factors and the risk of preeclampsia. *N. Engl. J. Med.* 350, 672–683. doi: 10.1056/NEJMoa031884

Li, H., Gu, B., Zhang, Y., Lewis, D. F., and Wang, Y. (2005). Hypoxia-induced increase in soluble Flt-1 production correlates with enhanced oxidative stress in trophoblast cells from the human placenta. *Placenta* 26, 210–217. doi: 10.1016/j.placenta.2004.05.004

Li, Z., Zhang, Y., Ying Ma, J., Kapoun, A. M., Shao, Q., Kerr, I., et al. (2007). Recombinant vascular endothelial growth factor 121 attenuates hypertension and improves kidney damage in a rat model of preeclampsia. *Hypertension* 50, 686–692. doi: 10.1161/HYPERTENSIONAHA.107.092098

Lisonkova, S., Sabr, Y., Mayer, C., Young, C., Skoll, A., and Joseph, K. S. (2014). Maternal morbidity associated with early-onset and late-onset preeclampsia. *Obstet. Gynecol.* 124, 771–781. doi: 10.1097/AOG.0000000000000472

Lhuba, E., Crispi, F., and Verlohren, S. (2015). Update on the pathophysiological implications and clinical role of angiogenic factors in pregnancy. *Fetal Diagn. Ther.* 37, 81–92. doi: 10.1159/000368605

Lyall, F. (2005). Priming and remodelling of human placental bed spiral arteries during pregnancy–a review. *Placenta* 26(Suppl. A), S31–S36. doi: 10.1016/j.placenta.2005.02.010

Maglione, D., Guerriero, V., Viglietto, G., Delli-Bovi, P., and Persico, M. G. (1991). Isolation of a human placenta cDNA coding for a protein related to the vascular permeability factor. *Proc. Natl. Acad. Sci. U.S.A.* 88, 9267–9271. doi: 10.1073/pnas.88.20.9267

March, M. I., Geahchan, C., Wenger, J., Raghuraman, N., Berg, A., Haddow, H., et al. (2015). Circulating angiogenic factors and the risk of adverse outcomes among haitian women with preeclampsia. *PLoS One* 10:e0126815. doi: 10.1371/journal.pone.0126815

Mastrogiannis, D. S., O'Brien, W. F., Krammer, J., and Benoit, R. (1991). Potential role of endothelin-1 in normal and hypertensive pregnancies. *Am. J. Obstet. Gynecol.* 165(6 Pt 1), 1711–1716. doi: 10.1016/0002-9378(91)90020-B

Matsubara, S., Bourdeau, A., terBrugge, K. G., Wallace, C., and Letarte, M. (2000). Analysis of endoglin expression in normal brain tissue and in cerebral arteriovenous malformations. *Stroke* 31, 2653–2660. doi: 10.1161/01.STR.31.11.2653

Maynard, S. E., Min, J. Y., Merchan, J., Lim, K. H., Li, J., Mondal, S., et al. (2003). Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J. Clin. Invest.* 111, 649–658. doi: 10.1172/JCI17189

McDonald, S. D., Han, Z., Walsh, M. W., Gerstein, H. C., and Devereaux, P. J. (2010). Kidney disease after preeclampsia: a systematic review and meta-analysis. *Am. J. Kidney Dis.* 55, 1026–1039. doi: 10.1053/j.ajkd.2009.12.036

McFarlane, A., and Scott, J. S. (1976). Pre-eclampsia/eclampsia in twin pregnancies. *J. Med. Genet.* 13, 208–211. doi: 10.1136/jmg.13.3.208

McKinney, E. T., Shoori, R., Hunt, R. S., Ahokas, R. A., and Sibai, B. M. (2000). Plasma, urinary, and salivary 8-epi-prostaglandin f2alpha levels in normotensive and preeclamptic pregnancies. *Am. J. Obstet. Gynecol.* 183, 874–877. doi: 10.1067/mob.2000.108877

Moffett, A., Hiby, S. E., and Sharkey, A. M. (2015). The role of the maternal immune system in the regulation of human birthweight. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 370:20140071. doi: 10.1098/rstb.2014.0071

Mongraw-Chaffin, M. L., Cirillo, P. M., and Cohn, B. A. (2010). Preeclampsia and cardiovascular disease death: prospective evidence from the child health

and development studies cohort. *Hypertension* 56, 166–171. doi: 10.1161/HYPERTENSIONAHA.110.150078

Mostello, D., Catlin, T. K., Roman, L., Holcomb, W. L., and Lee, T. (2002). Preeclampsia in the parous woman: Who is at risk? *Am. J. Obstet. Gynecol.* 187, 425–429. doi: 10.1067/mob.2002.123608

Muller-Deile, J., and Schiffer, M. (2011). Renal involvement in preeclampsia: similarities to VEGF ablation therapy. *J. Pregnancy* 2011:176973. doi: 10.1155/2011/176973

Nakakita, B., Mogami, H., Kondoh, E., Tsukamoto, T., Yanagita, M., and Konishi, I. (2015). Case of soluble fms-like tyrosine kinase 1 apheresis in severe pre-eclampsia developed at 15 weeks' gestation. *J. Obstet. Gynaecol. Res.* 41, 1661–1663. doi: 10.1111/jog.12760

Nevo, O., Soleymanlou, N., Wu, Y., Xu, J., Kingdom, J., Many, A., et al. (2006). Increased expression of sFlt-1 in in vivo and in vitro models of human placental hypoxia is mediated by HIF-1. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 291, R1085–R1093. doi: 10.1152/ajpregu.00794.2005

Norwitz, E. R., Schust, D. J., and Fisher, S. J. (2001)Implantation and the survival of early pregnancy. *N. Engl. J. Med.* 345, 1400–1408. doi: 10.1056/NEJMra000763

Onda, K., Tong, S., Beard, S., Binder, N., Muto, M., Senadheera, S. N., et al. (2017). Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. *Hypertension*, 69, 457–468. doi: 10.1161/HYPERTENSIONAHA.116.08408

Ozol, G., and Mandala, M. (2009). Maternal uterine vascular remodeling during pregnancy. *Physiology* 24, 58–71. doi: 10.1152/physiol.00033.2008

Palomaki, G. E., Haddow, J. E., Haddow, H. R., Salahuddin, S., Grahchan, C., Cardeira, A. S., et al. (2015). Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia. *Prenat. Diagn.* 35, 386–393. doi: 10.1002/pd.4554

Phipps, E., Prasanna, D., Brima, W., and Jim, B. (2016). Preeclampsia: updates in pathogenesis, definitions, and guidelines. *Clin. J. Am. Soc. Nephrol.* 11, 1102–1113. doi: 10.2215/CJN.12081115

Pijnenborg, R., Vercruysse, L., and Hanssens, M. (2006). The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta* 27, 939–958. doi: 10.1016/j.placenta.2005.12.006

Powe, C. E., Levine, R. J., and Karumanchi, S. A. (2011). Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation* 123, 2856–2869. doi: 10.1161/CIRCULATIONAHA.109.853127

Qu, R., Silver, M. M., and Letarte, M. (1998). Distribution of endoglin in early human development reveals high levels on endocardial cushion tissue mesenchyme during valve formation. *Cell Tissue Res.* 292, 533–543. doi: 10.1007/s004410051064

Rana, S., Powe, C. E., Salahuddin, S., Verlohren, S., Perschel, F. H., Levine, R. J., et al. (2012). Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation* 125, 911–919. doi: 10.1161/CIRCULATIONAHA.111.054361

Rana, S., Schnettler, W. T., Powe, C., Wenger, J., Salahuddin, S., Cardeira, A. S., et al. (2013). Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. *Hypertens. Pregnancy* 32, 189–201. doi: 10.3109/10641955.2013.784788

Red-Horse, K., Zhou, Y., Genbacev, O., Prakobphol, A., Foulk, R., McMaster, M., et al. (2004).Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. *J. Clin. Invest.* 114, 744–754. doi: 10.1172/JCI200422991

Roberts, J. M., and Lain, K. Y. (2002). Recent Insights into the pathogenesis of pre-eclampsia. *Placenta* 23, 359–372. doi: 10.1053/plac.2002.0819

Roberts, J. M., Taylor, R. N., Musci, T. J., Rodgers, G. M., Hubel, C. A., and McLaughlin, M. K. (1989). Preeclampsia: an endothelial cell disorder. *Am. J. Obstet. Gynecol.* 161, 1200–1204. doi: 10.1016/0002-9378(89)90665-0

Robertson, A. K., Rudling, M., Zhou, X., Gorelik, L., and Flavell, R. A., Hansson, G. K. (2003). Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. *J. Clin. Invest.* 112, 1342–1350. doi: 10.1172/JCI18607

Robinson, C. J., and Johnson, D. D. (2007). Soluble endoglin as a second-trimester marker for preeclampsia. *Am. J. Obstet. Gynecol.* 197, 174.e1–174.e5. doi: 10.1016/j.ajog.2007.03.058

Rolnik, D. L., Wright, D., Poon, L. C., O'Gorman, N., Syngelaki, A., Matallana, C. D., et al. (2017). Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N. Engl. J. Med.* 377, 613–622. doi: 10.1056/NEJMoa1704559

Romero, R., Nien, J. K., Espinoza, J., Todem, D., Fu, W., Chung, H., et al. (2008). A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. *J. Matern. Fetal Neonatal Med.* 21, 9–23. doi: 10.1080/14767050701830480

Saleh, L., Samantar, R., Garrelds, I. M., van den Meiracker, A. H., Visser, W., and Danser, A. H. J. (2017). Low soluble fms-like tyrosine kinase-1, endoglin, and endothelin-1 levels in women with confirmed or suspected preeclampsia using proton pump inhibitors. *Hypertension* 70, 594–600. doi: 10.1161/HYPERTENSIONAHA.117.09741

Saleh, L., Verdonk, K., Visser, W., van den Meiracker, A. H., and Danser A H. (2016). The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. *Ther. Adv. Cardiovasc. Dis.* 10, 282–293. doi: 10.1177/1753944715624853

Santner-Nanan, B., Peek, M. J., Khanam, R., Richarts, L., Zhu, E., Fazekas de St Groth, B., and Nanan R. (2009). Systemic increase in the ratio between Foxp3$^+$ and IL-17-producing CD4$^+$ T cells in healthy pregnancy but not in preeclampsia. *J. Immunol.* 183, 7023–7030. doi: 10.4049/jimmunol.0901154

Schrier, R. W. (1988). Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). *N. Engl. J. Med.* 319, 1127–1134. doi: 10.1056/NEJM198810273191705

Sibai, B. M., and Stella, C. L. (2009). Diagnosis and management of atypical preeclampsia-eclampsia. *Am. J. Obstet. Gynecol.* 200, 481.e1–481.e7. doi: 10.1016/j.ajog.2008.07.048

Siegar, M., Thadhani, R., and Karumanchi, S. A. (2015). Pathogenesis of preeclampsia. *Curr. Opin. Nephrol. Hypertens.* 24, 131–138. doi: 10.1097/MNH.0000000000000105

Sison, K., Eremina, V., Baelde, H., Min, W., Hirashima, M., Fantus, I. G., et al. (2010). Glomerular structure and function require paracrine, not autocrine, VEGF-VEGFR-2 signaling. *J. Am. Soc. Nephrol.* 21, 1691–1701. doi: 10.1681/ASN.2010030295

Skarzinski, G., Khamaisi, M., Burselyn, M., Mekler, J., Lan, D., Evdokimov, P., et al. (2009). Intrauterine growth restriction and shallower implantation site in rats with maternal hyperinsulinemia are associated with altered NOS expression. *Placenta* 30, 898–906. doi: 10.1016/j.placenta.2009.07.014

Sohlberg, S., Mulic-Lutvica, A., Lindgren, P., Ortiz-Nieto, F., Wikstrom, A. K., and Wikstrom J. (2014). Placental perfusion in normal pregnancy and early and late preeclampsia: a magnetic resonance imaging study. *Placenta* 35, 202–206. doi: 10.1016/j.placenta.2014.01.008

Son, G. H., Kwon, J. Y., Lee, S., Park, J., Kim, Y. J., Yun, B., et al. (2013). Comparison of serum and urinary nephrin levels between normal pregnancies and severe preeclampsia. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 166, 139–144. doi: 10.1016/j.ejogrb.2012.10.011

Sovio, U., Gaccioli, F., Cook, E., Hund, M., Charnock-Jones, D. S., and Smith, G. C. S. (2017). Prediction of preeclampsia using the soluble fms-like tyrosine kinase 1 to placental growth factor ratio: a prospective cohort study of unselected nulliparous women. *Hypertension* 69, 731–738. doi: 10.1161/HYPERTENSIONAHA.116.08620

Spargo, B., Mc, C. C., and Winemiller, R. (1959). Glomerular capillary endotheliosis in toxemia of pregnancy. *Arch. Pathol.* 68, 593–599.

Spradley, F. T., Tan, A. Y., Joo, W. S., Daniels, G., Kussie, P., Karumanchi, S. A., et al. (2016). Placental growth factor administration abolishes placental ischemia-induced hypertension. *Hypertension* 67, 740–747. doi: 10.1161/HYPERTENSIONAHA.115.06785

Staff, A. C., Benton, S. J., von Dadelszen, P., Roberts, J. M., Taylor, R. N., Powers, R. W., et al. (2013). Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 61, 932–942. doi: 10.1161/HYPERTENSIONAHA.111.00250

Takimoto, E., Ishida, J., Sugiyama, F., Horiguchi, H., Murakami, K., and Fukamizu, A. (1996). Hypertension induced in pregnant mice by placental renin and maternal angiotensinogen. *Science* 274, 995–998. doi: 10.1126/science.274.5289.995

Taylor, R. N., Grimwood, J., Taylor, R. S., McMaster, M. T., Fisher, S. J., and North, R. A. (2003). Longitudinal serum concentrations of placental growth factor: evidence for abnormal placental angiogenesis in pathologic pregnancies. *Am. J. Obstet. Gynecol.* 188, 177–182. doi: 10.1067/mob.2003.111

Journal of
Cardiovascular
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Review

Pre-Eclampsia and Eclampsia: An Update on the Pharmacological Treatment Applied in Portugal †

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Received: 11 December 2017; Accepted: 14 January 2018; Published: 17 January 2018

Abstract: Pre-eclampsia and eclampsia are two hypertensive disorders of pregnancy, considered major causes of maternal and perinatal death worldwide. Pre-eclampsia is a multisystemic disease characterized by the development of hypertension after 20 weeks of gestation, with the presence of proteinuria or, in its absence, of signs or symptoms indicative of target organ injury. Eclampsia represents the consequence of brain injuries caused by pre-eclampsia. The correct diagnosis and classification of the disease are essential, since the therapies for the mild and severe forms of pre-eclampsia are different. Thus, this review aims to describe the most advisable antepartum pharmacotherapy for pre-eclampsia and eclampsia applied in Portugal and based on several national and international available guidelines. Slow-release nifedipine is the most recommended drug for mild pre-eclampsia, and labetalol is the drug of choice for the severe form of the disease. Magnesium sulfate is used to prevent seizures caused by eclampsia. Corticosteroids are used for fetal lung maturation. Overall, the pharmacological prevention of these diseases is limited to low-dose aspirin, so it is important to establish the safest and most effective available treatment.

Keywords: pre-eclampsia; eclampsia; pharmacological therapy; pathophysiology; Portugal

1. Introduction

Pregnancy is characterized by significant metabolic and hemodynamic changes that begin early in the gestational period. Major hemodynamic changes include an increase in the cardiac output during the first trimester, sodium and water retention leading to plasma volume expansion with a peak around week 30, and reductions in the systemic vascular resistance and systemic blood pressure [1]. The reduction of the systemic vascular resistance is around 25% and is due to the increase in vasodilating agents, like nitric oxide and prostacyclin production, and the decrease in the sensitivity to norepinephrine and angiotensin [1]. The diastolic blood pressure begins to decrease from the 7th week of gestation, with a 10 mmHg decline between the 24th–26th gestation weeks, returning to normal values during the third trimester [2,3]. These are some of the changes that can occur during pregnancy. Hypertension is the most prevalent maternal complication worldwide (several studies estimate that it affects 7–10% of all pregnancies) [4,5], and it is associated with a significant morbidity and mortality of the mother and fetus. In fact, hypertension is the second largest cause of direct maternal death worldwide (14% of the total) [6], and it is estimated that 192 people die every day because of hypertensive disorders in pregnancy [7]. Pre-eclampsia and eclampsia are two hypertensive disorders of pregnancy, considered as major causes of maternal and perinatal morbidity and mortality [5]. These diseases affect between 3% and 5% of all pregnancies and account for more than 60,000 maternal and 500,000 fetal deaths per year worldwide [8]. It is known that pre-eclampsia and eclampsia are the hypertensive disorders that involve the most significant health risks for the

pregnant woman and the fetus. In this context, it is imperative to evaluate whether all possible and necessary measures are being taken correctly in terms of prevention, maintenance, and treatment of the disease. Gathering pharmacological information from Portuguese and International guidelines, the main purpose of this review is to describe the most recommended pharmacological treatments for these two hypertensive disorders in pregnant women during the gestational and antepartum period.

2. Methods

A literature review was performed based on the analysis of guidelines and papers available on PubMed. This search was carried out for pre-eclampsia, eclampsia, and for the pharmacological therapy, using different combinations of several keywords, such as pre-eclampsia, eclampsia, pharmacology, therapy, pregnancy diseases, pathophysiology, cardiovascular diseases (CVD), pregnancy, and hypertensive disorders of pregnancy, only present in the title, the abstract, or both. The search terms used were pre-eclampsia OR eclampsia AND pharmacology; pre-eclampsia OR eclampsia AND pathophysiology; pre-eclampsia OR eclampsia AND therapy; pregnancy diseases AND pre-eclampsia OR eclampsia; CVD AND pregnancy; hypertensive disorders of pregnancy AND pre-eclampsia OR eclampsia. From all the articles retrieved, unrelated, inaccessible, duplicate, and foreign language papers were excluded. The bibliographies of the articles used in this review were searched for additional relevant citations. The search was emphasized for the last six years (2011–2017), however, the results of the most important studies and those with greater relevance for this review are described below, and a weight-of-evidence approach was applied. In addition to PubMed, several documents and guidelines available from different national and international hospitals and organizations were also analyzed.

3. Pre-Eclampsia and Eclampsia

Pre-eclampsia is a multisystemic disease characterized by the development of hypertension after 20 weeks of gestation in a previously normotensive woman, with the presence of proteinuria or, in its absence, of signs or symptoms indicative of target organ injury [9]. The clinical signs involve multiple organs, including the liver, kidneys, heart, lungs, brain, and pancreas (Table 1). These complications can result in maternal and fetal adverse outcomes that can lead to intrauterine growth restriction, placental hypoperfusion, premature placental disruption or, in most serious situations, termination of pregnancy and fetal and maternal death [10,11].

This disease can be divided into mild and severe forms, according to the severity and type of the symptoms presented. The mild form of pre-eclampsia is characterized by systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg, and proteinuria >300 mg/24 h [12,13]. The severe form of pre-eclampsia is characterized by severe hypertension (SBP > 160 mmHg or DBP > 110 mmHg), or severe proteinuria (>2 g/24 h), or signs and symptoms of target organ damage [12,13]. Women with severe pre-eclampsia may present headaches, visual disturbances (including blindness), epigastric pain, nausea and vomits, hepatic and renal insufficiency, and pulmonary edema [14].

The incidence of pre-eclampsia is also explained by several risk factors (described in Table 2), that include maternal age under 20 years old or over 40 years old, history of pre-eclampsia, previous hypertension, autoimmune diseases, and obesity [15,16]. A woman is at moderate risk for pre-eclampsia if she has no more than one risk factor (Table 2); a woman is at high risk for pre-eclampsia if she has two or more risk factors for the disease [12,16]. According to this classification, the clinician will consider the prescription of low-dose aspirin to the patient (this will be discussed further in the results).

On another strand, a surprising discovery was made consisting in the demonstration that smoking protects pregnant women from developing pre-eclampsia [17], since smoking enhances the expression of ligands of the vascular endothelial growth factor (VEGF) family, which regulate the differentiation and survival of cytotrophoblasts, leading to normal uterine invasion [18]. Nonetheless, it is still not

recommended that pregnant women smoke, since smoking is a risk factor for several complications during pregnancy, namely miscarriages, placental abruption, preterm delivery, and reduced birth weight [18].

Table 1. Signs and symptoms of pre-eclampsia per organ system.

Systems	Signs/Symptoms
Central Nervous system	Headaches Visual disturbances Seizures (eclampsia)
Renal system	Proteinuria Oliguria Abnormal kidney tests Hypertension
Vascular system	Severe hypertension
Cardiorespiratory system	Chest pain Dyspnea Low oxygen saturation Pulmonary edema
Hepatic system	Abnormal liver function Epigastric pain Nausea
Hematologic system	Hemorrhage Coagulation impairment Intravascular disseminated coagulation Shock

Table 2. Summary of risk factors for pre-eclampsia.

Risk Factors for Pre-Eclampsia	Mean Relative Risk (95% Confidence Interval)	References
Antiphospholipid syndrome	9.72 (4.34–21.75)	
Relative risk of preeclampsia	7.19 (5.85–8.83)	
Previous pre-eclampsia	7.19 (5.85–8.83)	
Diabetes mellitus (type I or II)	3.56 (2.54–4.99)	
Multiple pregnancy	2.93 (2.04–4.21)	[16]
First pregnancy	2.91 (1.28–6.61)	
Familiar history of pre-eclampsia	2.90 (1.70–4.93)	
BMI $\geq$ 35 Kg/m^2	2.47 (1.66–3.67)	
Maternal age <20 or >40 years old	1.96 (1.34–2.87)	
Chronic hypertension	1.38 (1.01–1.87)	
Chronic autoimmune disease	6.9 (1.1–42.3)	[19]
Venous thromboembolism (VTE)	2.2 (1.3–3.7)	[20]
Intergestational interval $\geq$10 years	Similar to multiple pregnancy	[21]
Chronic kidney disease	1.70 (1.30–2.23) *	[22]

* Values for odd ratio.

Eclampsia represents the consequence of brain injuries caused by pre-eclampsia. It is defined as pre-eclampsia with the abrupt development of seizures or coma during the gestational period or post-partum, non-attributable to other neurologic diseases that can justify the convulsive state (namely epilepsy or cerebral stroke) [9]. Eclampsia is the rarest [23] and most severe [24] of all the hypertensive disorders of pregnancy, with a high maternal and fetal mortality [25].

Pre-eclampsia is associated with several complications not only during pregnancy but also in postpartum period. A broad diversity of studies has demonstrated that women who had pregnancies complicated with pre-eclampsia have, throughout live, a greater risk and incidence of cardiovascular

diseases, with an adjusted hazard ratio of 2.1 in a 95% confidence interval of 1.8–2.4 according to Ray and collaborators [26–28], major cardiovascular events, such as myocardial infarction (with an adjusted hazard ratio of 13.0 in a 95% confidence interval of 4.6–6.3), stroke (with an adjusted hazard ratio of 14.5 in a 95% confidence interval of 1.3–165.1), or heart failure (with an adjusted hazard ratio of 8.3 in a 95% confidence interval of 4.2–16.4) [29], and hospitalization related with cardiovascular events [30]. Children born from women who had pre-eclampsia during their pregnancies are also at a greater risk for cardiovascular events during their lifetime [31]. Other studies demonstrated an elevated blood pressure and body mass index in these children [32]. Therefore, pregnancy can be considered as a window for the future health of women and their children.

It is known that, currently, the only definitive cure for pre-eclampsia is the delivery of the fetus, and available therapies for this disease only have symptom management purposes [5]. For these reasons, it is of major importance that the pharmacological prophylaxis treatment is as effective and safe as possible to prevent severe forms of the disease and pre-eclampsia evolution to eclampsia, thus allowing the correct development and maturation of the fetus without risking the mother's health and well-being.

4. Pathophysiology

Although it is a well-studied disease, the pathophysiology of pre-eclampsia remains uncertain. Several key features are thought to have a role in the development of pre-eclampsia, which is mainly considered as a vascular disorder. The most probable causes for this disease are a failure of trophoblast invasion leading to a failed transformation of the uterine spiral arteries, and an incorrect deep placentation [33]. Trophoblasts are the first cells that differentiate from the fertilized egg, they form the outer membrane of the placenta, and are responsible for the nutrients and oxygen exchange between the mother and the fetus [13,34]. Also, decidual natural killer (NK) cells can regulate trophoblast invasion and vascular growth, two essential processes in placental development [35]. An abnormal expression of NK cell surface antigens and a failure in the regulation of NK cell cytotoxicity and cytokines or angiogenic factors may be some of the causes of pre-eclampsia [36], resulting in a high-flow and high-pressure state [13,37,38]. Consequently, there is a high risk for ischemia-reperfusion injury of the placenta because of the vasoconstriction of the maternal arteries, which will lead to the formation of reactive oxygen radicals and further endothelial dysfunction [13,38,39]. Thus, pre-eclampsia can be related with the excessive release of some mediators by the injured endothelial cells.

The excessive soluble fms-like tyrosine kinase (sFlt)-1 or endoglin and the reduced free placental growth factor (PlGF) constitute another hypothesis for the pathogenesis of preeclampsia, namely, the angiogenic imbalance [34]. When sFlt-1 levels, which is a variant for PlGF and VEGF, are increased there is an inactivation or decrease of PlGF and VEGF concentration, resulting in endothelial dysfunction [34]. In the case of endoglin, which is a surface coreceptor for the transforming growth factor β (TGFβ) family, soluble endoglin (sEng) binds to endothelial receptors and inhibits several TGFβ isoforms, resulting in a decreased endothelial nitric oxide (NO)-dependent vasodilatation [40]. Vascular endothelial cells collected from pre-eclamptic women or exposed to serum from pre-eclamptic pregnancies produce less NO than endothelial cells from normal pregnancies [41–43]. Akar et al. demonstrated that agonist-stimulated NO production is reduced in isolated umbilical arteries [43,44]. Other studies also reported a decrease in agonist-stimulated NO production in umbilical and hand vein endothelial cells derived from pre-eclamptic pregnancies, concluding that the production of NO is compromised also in the maternal systemic arterial and venous vasculature, and not only in the maternal uterine and umbilical vasculature [42,45–47].

Prostacyclin (PGI_2), another potent vasodilator, is decreased in pre-eclamptic women. This could be due to impaired endothelial Ca^{2+} signaling [42,43] and to the inhibition of PGI_2 production by reactive oxygen species (ROS) [43,48]. It is still unclear the role of endothelium-derived hyperpolarizing factor (EDHF) in the vascular pathogenesis of pre-eclampsia, however, EDHF-mediated vasorelaxation is reduced in vessels from pre-eclamptic pregnancies [47,49,50].

A subset of women with pre-eclampsia have detectable autoantibodies against type-1 angiotensin II receptor (AT_1) in the serum [51,52] which can activate AT_1 in endothelial cells, vascular smooth muscle cells, and mesangial cells from the kidney glomerulus. AT_1 autoantobodies have been shown to induce hypertension, proteinuria, glomerulus capillary endotheliosis, increased production of sVEGFR-1 (soluble Vascular Endothelial Growth Factor Receptor) and sEng, and to stimulate the synthesis of NADPH oxidase. These combined actions lead to oxidative stress, increased production of thrombin, fibrinolysis defect with fibrin deposition, and finally to an anti-angiogenic state [11,53,54]. Pre-eclampsia has also been associated with thrombocytopenia [55]. In fact, the role of platelet activation in pre-eclampsia has been evidenced through several features, including increased platelet size and reduced lifespan, increased maternal plasma levels of platelet factor 4 and β thromboglobulin, increased production of thromboxane B2 by platelets, and thrombi formation in the microcirculation of several target organs [11]. As it was mentioned before, PGl2, which has vasodilator actions and inhibits platelet aggregation, is decreased in women with pre-eclampsia, while thromboxane A2 is increased, leading to vasoconstriction and platelet aggregation. These will lead to vasospasm and platelet consumption, which are characteristic of pre-eclampsia [11]. Another important feature in pre-eclamptic women is the excessive thrombin generation. This may be due to different causes (endothelial cell dysfunction, platelet activation, chemotaxis of monocytes, proliferation of lymphocytes, neutrophil activation, or excessive generation of tissue factor in response to the activity of proinflammatory cytokines) ending in the deposition of fibrin in several organ systems [11]. Other factors have been implicated in the pathogenesis of pre-eclampsia, including genetic, environmental, and lifestyle factors. Genetic and environmental factors regulate several components that determine the susceptibility of a woman to the disease, like the predisposition to hypertensive disorders, autoimmune diseases, or diabetes (these factors predispose for pre-eclampsia) [11].

On the other hand, excessive weight (body mass index >35 Kg/m^2) is an important risk factor for the disease, with a relative risk of 1.96 in a 95% confidence interval of 1.34–2.87 [16,56]. Several studies have focused on the measurement of different biomarkers for pre-eclampsia, including maternal body mass index, concluding that overweight and obesity are among the most important risk factors for pre-eclampsia, with an attributable risk percent of 64.9% when compared to women with a normal body weight [1,57,58]. However, the mechanisms by which obesity increases the incidence of pre-eclampsia are still to be discovered, nonetheless, several hypotheses have arisen. It was proposed that maternal obesity may reduce cytotrophoblast migration and uterine spiral arteries remodeling, leading to placental ischemia. Also, obesity promotes the increase of circulating antiangiogenic factors and proinflammatory pathways by placental ischemia, leading to the reduction of vascular NO levels and the increase of peripheral resistance, which may lead to the development of pre-eclampsia. Obesity is not by itself the promotor of pre-eclampsia, but other metabolic abnormalities are mandatory for obesity to increase the risk pre-eclampsia [59].

Figure 1 summarizes the pathophysiology of the disease.

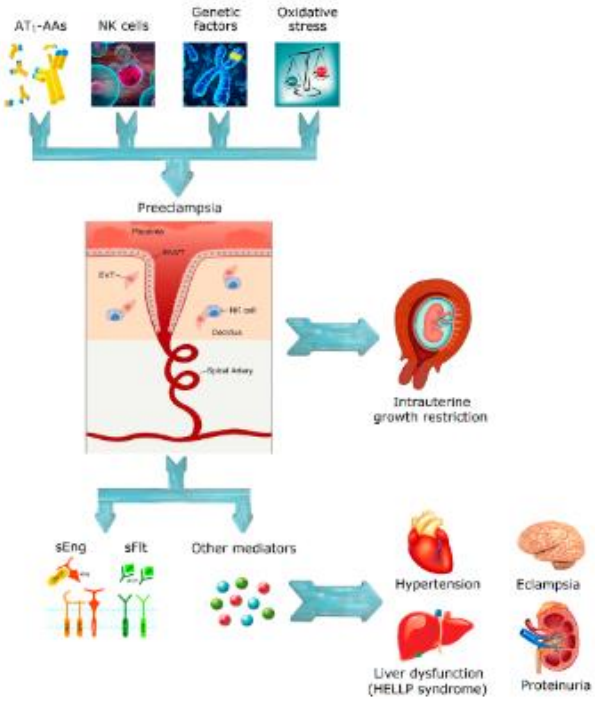


Figure 1. Proposed mechanism for pre-eclampsia and eclampsia.

5. Pharmacological Therapy

For the prevention of pre-eclampsia, the only effective therapy that is currently known is low-dose aspirin. Some international guidelines, including those from the World Health Organization (WHO), have reported that, from 12 weeks of gestation until delivery, a dose of 75–100 mg of aspirin should be prescribed [56,60]. However, some studies demonstrated the benefits of this therapy only in women at high risk for the disease, in whom aspirin reduces the risk of preterm pre-eclampsia and the incidence of severe pre-eclampsia [61,62]. More recently, Tong et al. concluded that the aspirin dose should be greater than 100 mg and that, according to a study performed by Meher and collaborators, starting the aspirin after 16 weeks gestation is still beneficial to prevent pre-eclampsia [63,64].

One of the guidelines used in a Portuguese hospital also suggests the intake of aspirin (100 mg) by pregnant women with more than one risk factor [12]. Other preventive measures, including magnesium supplementation, fish oil supplementation, and vitamins C, D, and E supplements, have been proposed but failed to demonstrate a real benefit and receive consensus within the scientific community [65]. Calcium supplementation is related to a reduction in the risk of pre-eclampsia and in preterm birth [66]. It is most effective in populations where dietary calcium ingestion is low (<600 mg/day, which can occur in some low—and middle-income countries)—in these cases, WHO recommends a daily supplement of 2 g of calcium per day [66,67]. Regarding lifestyle interventions, several studies found no benefits in sodium restriction, diet interventions, and regular physical exercise [62,68].

The correct diagnosis and classification of the disease is essential, since the pharmacological therapy for the mild and severe forms of pre-eclampsia are distinct. The management of mild pre-eclampsia is intended to prevent the evolution to severe pre-eclampsia, to establish the timing of delivery, and to evaluate fetal lung development. In the case of severe pre-eclampsia, the objectives are the prevention of eclampsia (seizures), a rigorous control of blood pressure, and the planning of delivery. The most recent studies failed to prove the benefits of an antihypertensive therapy in pregnant women with mild pre-eclampsia in which the blood pressure is between 140/90 mmHg–150/100 mmHg: in these cases, medical surveillance is the only recommended measure [10]. Most guidelines, including some used in Portugal, follow this advice, suggesting that an antihypertensive therapy should be initiated only if SBP > 150–160 mmHg or if DBP > 100–110 mmHg [12,65,69,70].

It should be noted that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARA) should be avoided during pregnancy because of their teratogenic effects [9,12]. Also, it is important to avoid sublingual drug formulations, since they induce a rapid antihypertensive effect and can cause hypoperfusion of maternal target organs and potentially impair uteroplacentary circulation [65].

6. Mild Pre-Eclampsia

First, it is important to differentiate first-line and second-line therapies. The first-line therapy is the one accepted as the best treatment for the disease. This therapy can also be called induction therapy, primary therapy, and primary treatment. The second-line therapy is the treatment that is given when the primary treatment does not work or stops working. For this disease, oral alpha-methyldopa, 250 mg (2–3 tablets/day) or oral nifedipine, 30–60 mg in slow-release forms (once daily) can be considered as first-line treatment. Nifedipine is a calcium channel blocker described as a safe, effective, and nonteratogenic drug [7,71]. Alpha-methyldopa is an α-adrenergic receptor agonist which is also an effective and safe drug in pregnancy, but the fact that it needs to be taken more than once daily is a disadvantage with respect to nifedipine. In Portugal, alpha-methyldopa is also used as a valid and safe alternative to the calcium channel blockers like nifedipine, being used as second-line therapy for mild pre-eclampsia [12]. The NICE (*National Institute for Health and Care Excellence*) and NHS (*National Health Services*) guidelines recommend oral labetalol for mild pre-eclampsia, since this drug is the only antihypertensive drug approved in United Kingdom for pregnancy [65]. However, other consulted guidelines recommended intravenous labetalol only for the severe form of the disease. Table 3 states a proposed pharmacotherapy for mild pre-eclampsia.

Table 3. Proposed pharmacotherapy for mild pre-eclampsia.

Mild Pre-Eclampsia		
Blood Pressure <150/100 mmHg	**Blood Pressure ≥150/100 and <160/110 mmHg**	
Expectant management. The pregnant woman should maintain:	**First line**	**Second line**
• Rigorous control of blood pressure • Bed rest • Evaluate the necessity for hospital admission	• **Nifedipine** per os, slow-release forms, 30–60 mg once a day (breakfast), max 120 mg/day	• **Methyldopa** per os, 250–500 mg, 2–3 times per day (max 2–3 g/day) • **Atenolol** per os, 50–100 mg/day

7. Severe Pre-Eclampsia

Because of the elevated risks that this form of the disease implies for the pregnant woman, it is recommended immediate hospital admission and continuous monitoring. The antihypertensive therapy should be started promptly, and the clinicians should check for signs of imminent eclampsia (if needed, they should start a prophylactic anticonvulsive therapy) [56]. The recommended first-line therapy, which is agreed by the several national and international guidelines analyzed, is intravenous labetalol [12,65,70]. The infusion should start with a bolus of 20 mg in 2 min, followed by doses

between 20–80 mg every 10 min (maximum cumulative dose: 300 mg) until the blood pressure is <150/100 mmHg. The normal maintenance dose is 6–8 mL/h. The objective is to maintain the blood pressure under the referred values [65]. Labetalol is an α1- and β-adrenergic antagonist, safe to use during pregnancy in situations of severe hypertension. This drug should not be used if the patient has asthma; alternatively, oral nifedipine, 10–20 mg in immediate-release forms, can be used. Intravenous hydralazine can also be used if the pregnant woman is refractory to either labetalol or nifedipine [12]. In Table 4, the proposed pharmacotherapy for severe pre-eclampsia is reported.

Table 4. Proposed pharmacotherapy for severe pre-eclampsia.

Severe Pre-Eclampsia		
First Line	**Second Line**	
Labetalol	**Nifedipine**	**Hydralazine**
• Initiate bolus 20 mg IV (2 min) • Repeat doses of 20–80 mg every 10 min (max cumulative dose: 300 mg) • Maintenance dose: 6–8 mL/h (adjust between 2–12 mL/h according to patient's evolution) from a concentration of 1 mg/mL	• 10–20 mg, immediate-release forms (never use sublingual administration)	• Bolus 5 mg IV (2 min) • Repeat doses every 20 min, until 20 mg total • Maintenance dose: 2 mg/h

8. Eclampsia

The anticonvulsive therapy is the most important therapy for eclampsia (Table 5). The recommended drug to use is intravenous magnesium sulfate. The infusion should start with a bolus of 4–6 g in 20 min, followed by a maintenance dose of 2–3 g (rate of 50–75 mL/h of 50 mg/mL in a physiologic solution or glucose solution). The therapy must be maintained for 24 h after the last convulsive state, or post-partum [12]. During the administration of this drug, it is important to control systemic magnesium levels to avoid any problems related to hypermagnesemia (in extreme cases, this can cause muscle paralysis and cardiorespiratory arrest), therefore, clinicians must constantly monitor the respiratory frequency, diuresis, and patellar reflexes [9]. Although not universally accepted, intravenous diazepam can be used as an alternative. This drug is related to greater fetal and maternal mortality and should only be used if the pregnant woman is refractory to magnesium sulfate [60]. In Portugal, several hospitals follow this treatment with diazepam only when magnesium sulfate is contraindicated [12,24,69,70].

Table 5. Proposed pharmacotherapy for eclampsia prophylaxis.

Eclampsia		
Magnesium Sulphate		
Loading Dose	**Maintenance Dose**	**"Booster" Dose (If Necessary)**
• 4–6 g IV, slow infusion (20 min) • 2–3 of 10 mL ampoules (20 mg/mL) in 100 mL of physiologic solution • Perfusion at 200–300 mL/h	• 2–3 g IV • 8 of 10 mL ampoules (50 mg/mL) in 1000 mL of physiologic solution or glucose solution • Perfusion at 50–75 mL/h, maintain for 24 h after birth of after last seizure	• 2 g IV, slow infusion (10 min) • 1 of 10 mL ampoule (20 mg/mL) if recurrent seizures
If magnesium sulphate is contraindicated or if the patient is refractory to this treatment: Diazepam, 5 mg IV (5 min), repeat until max dose (20 mg).		

It should be noted that, besides the anticonvulsive therapy, an antihypertensive therapy similar to the one recommended for severe pre-eclampsia is mandatory.

9. Corticosteroids

The use of corticosteroids has great importance in the successful outcome of pregnancy, since it helps the correct development of fetal lungs and is neuroprotective for preterm fetuses [72]. This therapy is especially useful and important in premature newborns, since it reduces the respiratory discomfort and insufficiency in the newborn and improves the fetal outcome [56,70]. Corticotherapy is therefore recommended to a pregnant woman between 24 and 36 weeks of gestation, for whom delivery is probable or planned in the next seven days (maximum) (see Table 6) [56,70]. The corticosteroids most commonly used are intramuscular (IM) betamethasone and intravenous (IV) dexamethasone. These two drugs have very similar security and efficiency indexes [56,70].

Table 6. Proposed pharmacotherapy for fetal lung maturation.

Corticosteroids for Fetal Lung Maturation	
Corticotherapy should only be recommended if: Gestational age between 24 and 36 weeks Birth is planned or likely to happen in 7 days (limit)	
Betamethasone	**Dexamethasone**
12 g IM, 2 doses with a 24 h interval.	10 mg IV, 2 doses with a 24 h interval.

10. Conclusions

The different guidelines available for the management of pre-eclampsia and eclampsia are not completely consensual in their content. The pharmacotherapy presented in this review is based on the recommendations from various guidelines for the disease, Portuguese and International. At present, the clinician's experience and the patient's symptoms and response to treatment are still the most important factors that determine the drug prescription.

Pre-eclampsia is still a serious threat, mainly in underdeveloped countries where its incidence and mortality rates are higher. In these countries, there is an urgent need in health policies to promote the proper care of women who suffer from this disease and to inform the populations about the alert signs and symptoms, and the risks of pre-eclampsia. In developed countries, the incidence of the disease has increased in the past years, but the negative outcomes for the mother and the fetus have decreased, as a result of the continuous improvement in hospital care and follow-up.

Apart from low-dose aspirin, there is still no effective preventive measure for all forms of pre-eclampsia, and the pharmacological management of the disease is the most important factor for the patient's and the fetus's well-being. Slow-release nifedipine is the most recommended drug for mild pre-eclampsia, alongside with alpha-methyldopa. For the severe form of the disease, labetalol is the recommended drug, being nifedipine and hydralazine the alternative drugs. For the prevention of seizures from eclampsia, magnesium sulfate is the drug of choice, and, in this case, although there is no established standard of care at this time, it is possible to use diazepam as an alternative. The administration of corticosteroids for fetal lung maturation has proven advantages in the fetal outcome and is recommended in pregnant women that are predicted to have a preterm delivery.

The importance of prescribing the correct therapy in pre-eclampsia and eclampsia is vital for mother and fetal outcomes, and all the hospital's professional healthcare team (nurses, clinicians, pharmacists) have the responsibility to promote the correct use of the recommended drugs. Thus, we can conclude that, although there is no national guideline that allows a standardized and uniform treatment in all Portuguese hospitals, the guidelines developed and followed by these same hospitals go according to some international guidelines. However, there are still many discrepancies, as has been mentioned, and it would be worth adding a guideline whereby the professional healthcare team could be guided for a better health and prognosis of the patients.

Acknowledgments: We thank the Fundação para a Ciência e a Tecnologia (Portugal) for supporting the grant PEst-OE/SAU/UI0709/2014 and for supporting the grant UID/MULTI/00709/2013.

Author Contributions: G.M.P. was involved in the conception, acquisition of data, and writing of this manuscript. M.M. was involved in the writing and revision of this article. E.C. revised it critically for important intellectual content and gave the final approval. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gongora, M.C.; Wenger, N.K. Cardiovascular complications of pregnancy. *Int. J. Mol. Sci.* **2015**, *16*, 23905–23928. [CrossRef] [PubMed]
2. Flack, J.M.; Peters, R.; Mehra, V.C.; Nasser, S.A. Hypertension in special populations. *Cardiol. Clin.* **2002**, *20*, 303–319. [CrossRef]
3. Mustafa, R.; Ahmed, S.; Gupta, A.; Venuto, R.C. A comprehensive review of hypertension in pregnancy. *J. Pregnancy* **2012**, *2012*, 105918. [CrossRef] [PubMed]
4. Ahmad, A.S.; Samuelsen, S.O. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: A population study of 2 121 371 pregnancies. *BJOG* **2012**, *119*, 1521–1528. [CrossRef] [PubMed]
5. Lindheimer, M.D.; Taler, S.J.; Cunningham, F.G. Hypertension in pregnancy. *J. Am. Soc. Hypertens.* **2010**, *4*, 68–78. [CrossRef] [PubMed]
6. Say, L.; Chou, D.; Gemmill, A.; Tuncalp, O.; Moller, A.B.; Daniels, J.; Gulmezoglu, A.M.; Temmerman, M.; Alkema, L. Global causes of maternal death: A who systematic analysis. *Lancet Glob. Health* **2014**, *2*, e323–e333. [CrossRef]
7. Folic, M.; Folic, N.; Varjacic, M.; Jakovljevic, M.; Jankovic, S. Antihypertensive drug therapy for hypertensive disorders in pregnancy. *Acta Med. Median.* **2008**, *47*, 65–72.
8. Kuklina, E.V.; Ayala, C.; Callaghan, W.M. Hypertensive disorders and severe obstetric morbidity in the united states. *Obstet. Gynecol.* **2009**, *113*, 1299–1306. [CrossRef] [PubMed]
9. Moussa, H.N.; Arian, S.E.; Sibai, B.M. Management of hypertensive disorders in pregnancy. *Womens Health* **2014**, *10*, 385–404. [CrossRef] [PubMed]
10. Siqueira, F.; Moura, T.R.; Silva, S.S.; Peraçoli, J.C. Medicamentos anti-hipertensivos na gestação e puerpério. *Complementos Ciências Saúde* **2011**, *22*, 55–68.
11. Chaiworapongsa, T.; Chaemsaithong, P.; Yeo, L.; Romero, R. Pre-eclampsia part 1: Current understanding of its pathophysiology. *Nat. Rev. Nephrol.* **2014**, *10*, 466–480. [CrossRef] [PubMed]
12. Silva, V.; Palmira, J. Distúrbios hipertensivos. In *CHTV, EPE—Hospital são Teotónio, Viseu. Departamento de Obstetrícia e Ginecologia: Normas de Orientação Clínica*, 1st ed.; Martins, N.N., Verissimo, R., Eds.; Richter, G.: Viseu, Portugal, 2014; pp. 257–278.
13. Dhariwal, N.K.; Lynde, G.C. Update in the management of patients with preeclampsia. *Anesthesiol. Clin.* **2016**, *35*, 95–106. [CrossRef] [PubMed]
14. ACOG Committee on Obstetric Practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American college of obstetricians and gynecologists. *Int. J. Gynaecol. Obstet.* **2002**, *77*, 67–75.
15. Grand'Maison, S.; Pilote, L.; Okano, M.; Landry, T.; Dayan, N. Markers of vascular dysfunction after hypertensive disorders of pregnancy: A systematic review and meta-analysis. *Hypertension* **2016**, *68*, 1447–1458. [CrossRef] [PubMed]
16. English, F.A.; Kenny, L.C.; McCarthy, F.P. Risk factors and effective management of preeclampsia. *Integr. Blood Press Control* **2015**, *8*, 7–12. [PubMed]
17. Xiong, X.; Wang, F.L.; Davidge, S.T.; Demianczuk, N.N.; Mayes, D.C.; Olson, D.M.; Saunders, L.D. Maternal smoking and preeclampsia. *J. Reprod. Med.* **2000**, *45*, 727–732. [PubMed]
18. Zdravkovic, T.; Genbacev, O.; McMaster, M.T.; Fisher, S.J. The adverse effects of maternal smoking on the human placenta: A review. *Placenta* **2005**, *26* (Suppl. A), S81–S86. [CrossRef] [PubMed]
19. Stamilio, D.M.; Sehdev, H.M.; Morgan, M.A.; Propert, K.; Macones, G.A. Can antenatal clinical and biochemical markers predict the development of severe preeclampsia? *Am. J. Obstet. Gynecol.* **2000**, *182*, 589–594. [CrossRef] [PubMed]

20. Bellamy, L.; Casas, J.P.; Hingorani, A.D.; Williams, D.J. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. *BMJ* **2007**, *335*, 974. [CrossRef] [PubMed]
21. Skjaerven, R.; Wilcox, A.J.; Lie, R.T. The interval between pregnancies and the risk of preeclampsia. *N. Engl. J. Med.* **2002**, *346*, 33–38. [CrossRef] [PubMed]
22. Ayansina, D.; Black, C.; Hall, S.J.; Marks, A.; Millar, C.; Prescott, G.J.; Wilde, K.; Bhattacharya, S. Long term effects of gestational hypertension and pre-eclampsia on kidney function: Record linkage study. *Pregnancy Hypertens.* **2016**, *6*, 344–349. [CrossRef] [PubMed]
23. Povoa, A.M.; Costa, F.; Rodrigues, T.; Patricio, B.; Cardoso, F. Prevalence of hypertension during pregnancy in portugal. *Hypertens. Pregnancy* **2008**, *27*, 279–284. [CrossRef] [PubMed]
24. Campos, D.A.; Silva, I.S.; Costa, F.J. Eclâmpsia. In *Emergências Obstétricas*, 1st ed.; LIDEL, Ed.; Elsevier: Amsterdam, The Netherlands, 2011; pp. 77–87.
25. Société française d'anesthésie et de réanimation (Sfar); Collège national des gynécologues et obstétriciens français (CNGOF); Société française de médecine périnatale (SFMP); Société française de néonatalogie (SFNN). [multidisciplinary management of severe pre-eclampsia (PE). Experts' guidelines 2008. Societe francaise d'anesthesie et de reanimation. College national des gynecologues et obstetriciens francais. Societe francaise de medecine perinatale. Societe francaise de neonatalogie]. *Ann. Fr. Anesth. Reanim.* **2009**, *28*, 275–281.
26. Stekkinger, E.; Zandstra, M.; Peeters, L.L.; Spaanderman, M.E. Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome. *Obstet. Gynecol.* **2009**, *114*, 1076–1084. [CrossRef] [PubMed]
27. Ray, J.G.; Vermeulen, M.J.; Schull, M.J.; Redelmeier, D.A. Cardiovascular health after maternal placental syndromes (champs): Population-based retrospective cohort study. *Lancet* **2005**, *366*, 1797–1803. [CrossRef]
28. Enkhmaa, D.; Wall, D.; Mehta, P.K.; Stuart, J.J.; Rich-Edwards, J.W.; Merz, C.N.; Shufelt, C. Preeclampsia and vascular function: A window to future cardiovascular disease risk. *J. Womens Health* **2016**, *25*, 284–291. [CrossRef] [PubMed]
29. Lin, Y.S.; Tang, C.H.; Yang, C.Y.; Wu, L.S.; Hung, S.T.; Hwa, H.L.; Chu, P.H. Effect of pre-eclampsia-eclampsia on major cardiovascular events among peripartum women in taiwan. *Am. J. Cardiol.* **2011**, *107*, 325–330. [CrossRef] [PubMed]
30. Kestenbaum, B.; Seliger, S.L.; Easterling, T.R.; Gillen, D.L.; Critchlow, C.W.; Stehman-Breen, C.O.; Schwartz, S.M. Cardiovascular and thromboembolic events following hypertensive pregnancy. *Am. J. Kidney Dis.* **2003**, *42*, 982–989. [CrossRef] [PubMed]
31. Kajantie, E.; Eriksson, J.G.; Osmond, C.; Thornburg, K.; Barker, D.J. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: The helsinki birth cohort study. *Stroke* **2009**, *40*, 1176–1180. [CrossRef] [PubMed]
32. Davis, E.F.; Lazdam, M.; Lewandowski, A.J.; Worton, S.A.; Kelly, B.; Kenworthy, Y.; Adwani, S.; Wilkinson, A.R.; McCormick, K.; Sargent, I.; et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: A systematic review. *Pediatrics* **2012**, *129*, e1552–e1561. [CrossRef] [PubMed]
33. Fisher, S.J. Why is placentation abnormal in preeclampsia? *Am. J. Obstet. Gynecol.* **2015**, *213*, S115–S122. [CrossRef] [PubMed]
34. Gathiram, P.; Moodley, J. Pre-eclampsia: Its pathogenesis and pathophysiolgy. *Cardiovasc. J. Afr.* **2016**, *27*, 71–78. [CrossRef] [PubMed]
35. Hanna, J.; Goldman-Wohl, D.; Hamani, Y.; Avraham, I.; Greenfield, C.; Natanson-Yaron, S.; Prus, D.; Cohen-Daniel, L.; Arnon, T.I.; Manaster, I.; et al. Decidual nk cells regulate key developmental processes at the human fetal-maternal interface. *Nat. Med.* **2006**, *12*, 1065–1074. [CrossRef] [PubMed]
36. Fukui, A.; Yokota, M.; Funamizu, A.; Nakamua, R.; Fukuhara, R.; Yamada, K.; Kimura, H.; Fukuyama, A.; Kamoi, M.; Tanaka, K.; et al. Changes of nk cells in preeclampsia. *Am. J. Reprod. Immunol.* **2012**, *67*, 278–286. [CrossRef] [PubMed]
37. Tessier, D.R.; Yockell-Lelievre, J.; Gruslin, A. Uterine spiral artery remodeling: The role of uterine natural killer cells and extravillous trophoblasts in normal and high-risk human pregnancies. *Am. J. Reprod. Immunol.* **2015**, *74*, 1–11. [CrossRef] [PubMed]
38. Burton, G.J.; Woods, A.W.; Jauniaux, E.; Kingdom, J.C. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta* **2009**, *30*, 473–482. [CrossRef] [PubMed]

39. Hung, T.H.; Skepper, J.N.; Burton, G.J. In vitro ischemia-reperfusion injury in term human placenta as a model for oxidative stress in pathological pregnancies. *Am. J. Pathol.* **2001**, *159*, 1031–1043. [CrossRef]
40. Malik, R.; Kumar, V. Hypertension in pregnancy. *Adv. Exp. Med. Biol.* **2017**, *956*, 375–393. [PubMed]
41. Hayman, R.; Warren, A.; Brockelsby, J.; Johnson, I.; Baker, P. Plasma from women with pre-eclampsia induces an in vitro alteration in the endothelium-dependent behaviour of myometrial resistance arteries. *BJOG* **2000**, *107*, 108–115. [CrossRef] [PubMed]
42. Krupp, J.; Boeldt, D.S.; Yi, F.X.; Grummer, M.A.; Bankowski Anaya, H.A.; Shah, D.M.; Bird, I.M. The loss of sustained Ca^{2+} signaling underlies suppressed endothelial nitric oxide production in preeclamptic pregnancies: Implications for new therapy. *Am. J. Physiol. Heart Circ. Physiol.* **2013**, *305*, H969–H979. [CrossRef] [PubMed]
43. Goulopoulou, S. Maternal vascular physiology in preeclampsia. *Hypertension* **2017**, *70*, 1066–1073. [CrossRef] [PubMed]
44. Akar, F.; Ark, M.; Uydes, B.S.; Soysal, M.E.; Saracoglu, F.; Abacioglu, N.; Van de Voorde, J.; Kanzik, I. Nitric oxide production by human umbilical vessels in severe pre-eclampsia. *J. Hypertens.* **1994**, *12*, 1235–1241. [CrossRef] [PubMed]
45. Steinert, J.R.; Wyatt, A.W.; Poston, L.; Jacob, R.; Mann, G.E. Preeclampsia is associated with altered Ca^{2+} regulation and no production in human fetal venous endothelial cells. *FASEB J.* **2002**, *16*, 721–723. [CrossRef] [PubMed]
46. Mahdy, Z.; Otun, H.A.; Dunlop, W.; Gillespie, J.I. The responsiveness of isolated human hand vein endothelial cells in normal pregnancy and in pre-eclampsia. *J. Physiol.* **1998**, *508 Pt 2*, 609–617. [CrossRef] [PubMed]
47. Boeldt, D.S.; Bird, I.M. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. *J. Endocrinol.* **2017**, *232*, R27–R44. [CrossRef] [PubMed]
48. Davidge, S.T.; Everson, W.V.; Parisi, V.M.; McLaughlin, M.K. Pregnancy and lipid peroxide-induced alterations of eicosanoid-metabolizing enzymes in the aorta of the rat. *Am. J. Obstet. Gynecol.* **1993**, *169*, 1338–1344. [CrossRef]
49. Luksha, L.; Agewall, S.; Kublickiene, K. Endothelium-derived hyperpolarizing factor in vascular physiology and cardiovascular disease. *Atherosclerosis* **2009**, *202*, 330–344. [CrossRef] [PubMed]
50. Luksha, L.; Nisell, H.; Luksha, N.; Kublickas, M.; Hultenby, K.; Kublickiene, K. Endothelium-derived hyperpolarizing factor in preeclampsia: Heterogeneous contribution, mechanisms, and morphological prerequisites. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2008**, *294*, R510–R519. [CrossRef] [PubMed]
51. Wallukat, G.; Homuth, V.; Fischer, T.; Lindschau, C.; Horstkamp, B.; Jupner, A.; Baur, E.; Nissen, E.; Vetter, K.; Neichel, D.; et al. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin at1 receptor. *J. Clin. Investig.* **1999**, *103*, 945–952. [CrossRef] [PubMed]
52. Harmon, A.C.; Cornelius, D.C.; Amaral, L.M.; Faulkner, J.L.; Cunningham, M.W., Jr.; Wallace, K.; LaMarca, B. The role of inflammation in the pathology of preeclampsia. *Clin. Sci.* **2016**, *130*, 409–419. [CrossRef] [PubMed]
53. Parrish, M.R.; Murphy, S.R.; Rutland, S.; Wallace, K.; Wenzel, K.; Wallukat, G.; Keiser, S.; Ray, L.F.; Dechend, R.; Martin, J.N.; et al. The effect of immune factors, tumor necrosis factor-alpha, and agonistic autoantibodies to the angiotensin ii type i receptor on soluble fms-like tyrosine-1 and soluble endoglin production in response to hypertension during pregnancy. *Am. J. Hypertens.* **2010**, *23*, 911–916. [CrossRef] [PubMed]
54. Xia, Y.; Kellems, R.E. Angiotensin receptor agonistic autoantibodies and hypertension: Preeclampsia and beyond. *Circ. Res.* **2013**, *113*, 78–87. [CrossRef] [PubMed]
55. Yan, M.; Malinowski, A.K.; Shehata, N. Thrombocytopenic syndromes in pregnancy. *Obstet. Med.* **2016**, *9*, 15–20. [CrossRef] [PubMed]
56. National Institute for Health and Care Exellence (NICE). *Severe Hypertension, Severe Pre-Eclampsia and Eclampsia in Critical Care—Nice Clinical Guideline*; Royal College of Obstetricians and Gynaecologists: London, UK, 2015.
57. Kenny, L.C.; Black, M.A.; Poston, L.; Taylor, R.; Myers, J.E.; Baker, P.N.; McCowan, L.M.; Simpson, N.A.; Dekker, G.A.; Roberts, C.T.; et al. Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: The screening for pregnancy endpoints (scope) international cohort study. *Hypertension* **2014**, *64*, 644–652. [CrossRef] [PubMed]

58. Pare, E.; Parry, S.; McElrath, T.F.; Pucci, D.; Newton, A.; Lim, K.H. Clinical risk factors for preeclampsia in the 21st century. *Obstet. Gynecol.* **2014**, *124*, 763–770. [CrossRef] [PubMed]
59. Spradley, F.T. Metabolic abnormalities and obesity's impact on the risk for developing preeclampsia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2016**, *312*, R5–R12. [CrossRef] [PubMed]
60. WHO. *Who Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia*, 2013/06/07 ed.; World Health Organization, Ed.; World Health Organization: Geneva, Switzerland, 2011; pp. 8–27.
61. Roberge, S.; Villa, P.; Nicolaides, K.; Giguere, Y.; Vainio, M.; Bakthi, A.; Ebrashy, A.; Bujold, E. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: A systematic review and meta-analysis. *Fetal Diagn. Ther.* **2012**, *31*, 141–146. [CrossRef] [PubMed]
62. Mol, B.W.; Roberts, C.T.; Thangaratinam, S.; Magee, L.A.; de Groot, C.J.; Hofmeyr, G.J. Pre-eclampsia. *Lancet* **2015**, *387*, 999–1011. [CrossRef]
63. Tong, S.; Mol, B.W.; Walker, S.P. Preventing preeclampsia with aspirin: Does dose or timing matter? *Am. J. Obstet. Gynecol.* **2017**, *216*, 95–97. [CrossRef] [PubMed]
64. Meher, S.; Duley, L.; Hunter, K.; Askie, L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: An individual participant data meta-analysis. *Am. J. Obstet. Gynecol.* **2017**, *216*, 121–128.e2. [CrossRef] [PubMed]
65. National Collaborating Centre for Women's and Children's Health. *Hypertension in Pregnancy: The Management of Hypertensive Disorders during Pregnancy—Nice Clinical Guideline*, 2012/01/06 ed.; Royal College of Obstetricians and Gynaecologists: London, UK, 2010.
66. Hofmeyr, G.J.; Lawrie, T.A.; Atallah, A.N.; Duley, L.; Torloni, M.R. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst. Rev.* **2014**, CD001059. [CrossRef]
67. WHO. *Guideline: Calcium Supplementation in Pregnant Women*, 2013/09/06 ed.; World Health Organization, Ed.; World Health Organization: Geneva, Switzerland, 2013; pp. 2–3.
68. Inversetti, A.; Smid, M.; Candiani, M.; Ferrari, M.; Galbiati, S. Predictive biomarkers of pre-eclampsia and effectiveness of preventative interventions for the disease. *Expert Opin. Biol. Ther.* **2014**, *14*, 1161–1173. [CrossRef] [PubMed]
69. Montenegro, N.; Campos, D.A.; Rodrigues, T.; Ramalho, C.; Silva, J.L.; Machado, A.P. Pré-eclâmpsia: Vigilância e tratamento. In *Protocolos de Medicina Materno-Fetal*, 3rd ed.; LIDEL, Ed.; LIDEL: Lisboa, Portugal, 2014; pp. 122–129.
70. Júlio, C.; Francisco, C.; Dias, E.; Campos, A. Pré-eclâmpsia. In *Protocolos de Atuação da Maternidade dr. Alfredo da Costa*, 2nd ed.; LIDEL, Ed.; LIDEL: Lisboa, Portugal, 2011; pp. 39–48.
71. Podymow, T.; August, P. Antihypertensive drugs in pregnancy. *Semin. Nephrol.* **2011**, *31*, 70–85. [CrossRef] [PubMed]
72. Bouet, P.E.; Brun, S.; Madar, H.; Baisson, A.L.; Courtay, V.; Gascoin-Lachambre, G.; Lasocki, S.; Sentilhes, L. Implementation of an antenatal magnesium sulfate protocol for fetal neuroprotection in preterm infants. *Sci. Rep.* **2015**, *5*, 14732. [CrossRef] [PubMed]

Taylor, R. N., Varma, M., Teng, N. N. H., and Roberts, J. M. (1990). Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. *J. Clin. Endocrinol. Metab.* 71, 1675–1677. doi: 10.1210/jcem-71-6-1675

Thadhani, R., Hagmann, H., Schaarschmidt, W., Roth, B., Cingoez, T., Karumanchi, S. A., et al. (2016). Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J. Am. Soc. Nephrol.* 27, 903–913. doi: 10.1681/ASN.2015020157

Thadhani, R., Kisner, T., Hagmann, H., Bossung, V., Noack, S., Schaarschmidt, W., et al. (2011). Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. *Circulation* 124, 940–950. doi: 10.1161/CIRCULATIONAHA.111.034793

Tjoa, M. L., Levine, R. J., and Karumanchi, S. A. (2007). Angiogenic factors and preeclampsia. *Front. Biosci.* 12, 2395–2402. doi: 10.2741/2241

Venkatesha, S., Toporsian, M., Lam, C., Hanai, J., Mammoto, T., Kim, Y. M., et al. (2006). Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat. Med.* 12, 642–649. doi: 10.1038/nm1429

Verdonk, K., Saleh, L., Lankhorst, S., Smilde, J. E., van Ingen, M. M., Garrelds, I. M., et al. (2015). Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin-angiotensin-aldosterone system suppression. *Hypertension* 65, 1316–1323. doi: 10.1161/HYPERTENSIONAHA.115.05267

Veron, D., Villegas, G., Aggarwal, P. K., Bertuccio, C., Jimenez, J., Velazquez, H., et al. (2012). Acute podocyte vascular endothelial growth factor (VEGF-A) knockdown disrupts alphaVbeta3 integrin signaling in the glomerulus. *PLoS One* 7:e40589. doi: 10.1371/journal.pone.0040589

Vikse, B. E., Irgens, L. M., Karumanchi, S. A., Thadhani, R., Reisaeter, A. V., and Skjaerven, R. (2012). Familial factors in the association between preeclampsia and later ESRD. *Clin. J. Am. Soc. Nephrol.* 7, 1819–1826. doi: 10.2215/CJN.01820212

Vikse, B. E., Irgens, L. M., Leivestad, T., Skjaerven, R., and Iversen, B. M. (2008). Preeclampsia and the risk of end-stage renal disease. *N. Engl. J. Med.* 359, 800–809. doi: 10.1056/NEJMoa0706790

Wang, I. K., Muo, C. H., Chang, Y. C., Liang, C. C., Chang, C. T., Lin, S. Y., et al. (2013). Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. *Can. Med. Assoc. J.* 185, 207–213. doi: 10.1503/cmaj.120230

Wang, Y., Zhao, S., Loyd, S., and Groome, L. J. (2012). Increased urinary excretion of nephrin, podocalyxin, and betaig-h3 in women with preeclampsia. *Am. J. Physiol. Renal Physiol.* 302, F1084–F1089. doi: 10.1152/ajprenal.00597.2011

Yoshida, A., Nakao, S., Kobayashi, M., and Kobayashi, H. (2000). Flow-mediated vasodilation and plasma fibronectin levels in preeclampsia. *Hypertension* 36, 400–404. doi: 10.1161/01.HYP.36.3.400

Young, B. C., Levine, R. J., and Karumanchi, S. A. (2010). Pathogenesis of preeclampsia. *Annu. Rev. Pathol.* 5, 173–192. doi: 10.1146/annurev-pathol-121808-102149

Yung, H. W., Atkinson, D., Campion-Smith, T., Olovsson, M., Charnock-Jones, D. S., and Burton, G. J. (2005). Differential activation of placental unfolded protein response pathways implies heterogeneity in causation of early- and late-onset pre-eclampsia. *J. Pathol.* 234, 262–276.

Zeisler, H., Llurba, E., Chantraine, F., Vatish, M., Staff, A. C., Sennstrom, M., et al. (2016). Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N. Engl. J. Med.* 374, 13–22. doi: 10.1056/NEJMoa1414838

Zhao, S., Gu, X., Groome, L. J., and Wang, Y. (2009). Decreased nephrin and GLEPP-1, but increased VEGF, Flt-1, and nitrotyrosine, expressions in kidney tissue sections from women with preeclampsia. *Reprod. Sci.* 16, 970–979. doi: 10.1177/1933719109338630

Zhao, S., Gu, Y., Coates, G., Groome, L. J., Salsem, M. A., Mathiesun, P. W., et al. (2011). Altered nephrin and podoplanin distribution is associated with disturbed polarity protein PARD-3 and PARD-6 expressions in podocytes from preeclampsia. *Reprod. Sci.* 18, 772–780. doi: 10.1177/1933719111398145

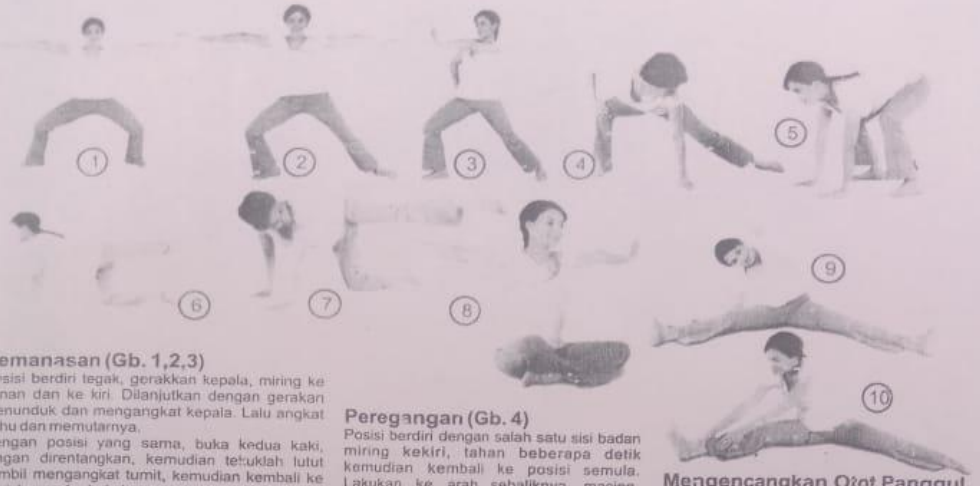
Zhou, C. C., Irani, R. A., Zhang, Y., Blackwell, S. C., Mi, T., Wen, J., et al. (2010). Angiotensin receptor agonistic autoantibody-mediated tumor necrosis factor-alpha induction contributes to increased soluble endoglin production in preeclampsia. *Circulation* 121, 436–444. doi: 10.1161/CIRCULATIONAHA.109.902890

Zhou, C. C., Zhang, Y., Irani, R. A., Zhang, H., Mi, T., Popek, E. J., et al. (2008). Angiotensin receptor agonistic autoantibodies induce pre-eclampsia in pregnant mice. *Nat. Med.* 14, 855–862. doi: 10.1038/nm.1856

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Lampiran 6. Leaflet Senam Nifas

SENAM IBU NIFAS



Pemanasan (Gb. 1,2,3)

Posisi berdiri tegak, gerakkan kepala, miring ke kanan dan ke kiri. Dilanjutkan dengan gerakan menunduk dan mengangkat kepala. Lalu angkat bahu dan memutarnya.

Dengan posisi yang sama, buka kedua kaki, tangan direntangkan, kemudian tekuklah lutut sambil mengangkat tumit, kemudian kembali ke posisi semula. Lakukan gerakan masing-masing 8x.

Posisi berdiri dengan lutut ditekuk, lakukan gerakan menekuk pergelangan tangan ke atas dan ke bawah 8x. Lanjutkan dengan memutar pergelangan tangan dari luar ke dalam, dan sebaliknya masing-masing 8x. Posisi berdiri tegak perut dikencangkan, ayunkan badan ke kanan dan ke kiri 8x. Masih berdiri tegak dan perut dikencangkan, tangan diayun-ayunkan. Dengan kaki terbuka. Lakukan gerakan seperti mendorong ke arah serong ke arah kiri dan sebaliknya. Lakukan gerakan 8x.

Mengencangkan Otot Paha (Gb. 6,7)

Posisi tetap seperti merangkak. Dorong salah satu kaki ke belakang tanpa menyentuh lantai. Lakukan juga untuk kaki yang lainnya. Masing-masing gerakan 8x. Posisi tetap merangkak, dorong salah satu kaki ke samping. Lakukan gerakan yang sama untuk kaki yang lainnya. Masing-masing 8x.

Peregangan (Gb. 4)

Posisi berdiri dengan salah satu sisi badan miring kekiri, tahan beberapa detik kemudian kembali ke posisi semula. Lakukan ke arah sebaliknya, masing-masing gerakan 8x. Tekuklah kaki (miring ke kiri), lalu ayunkan tangan lurus ke samping. Lakukan gerakan ke arah sebaliknya. Lakukan masing-masing 8x. Kaki dibuka pandangan ke bawah. Tekuk kaki kiri sambil mengayunkan tangan kanan hingga menyentuh kaki kiri, dan sebaliknya. Lakukan masing-masing 8x.

GERAKAN INTI

Memutar Lengan (Gb. 8)

Posisi duduk bersila Rentangkan tangan, lalu putarlah pergelangan tangan, lengan dan bahu. Lakukan gerakan dengan cepat sambil mengencangkan perut.

Mengencangkan Paha Dan Betis (Gb. 11, 12, 13)

Posisi tidur miring ke kanan. Angkat kaki atas. Kemudian turunkan perlahan-lahan. Lanjutkan dengan memutar pergelangan kaki, lakukan gerakan kombinasi dengan mengangkat kaki ke atas, putar pergelangan kaki, lalu turun perlahan-lahan. Lakukan juga untuk posisi sebaliknya. Masih dengan posisi tidur miring, ayunkan kaki depan bersamaan dengan tangan ke arah yang berlawanan. Lakukan juga untuk posisi sebaliknya, masing-masing 8x. Posisi tidur terlentang, ayunkan kaki naik turun. Lanjutkan dengan gerakan mengangkat salah satu kaki, bergantian. Lakukan 8x.

Mengencangkan Otot Panggul (Gb. 5)

Posisi seperti jongkok dengan telapak tangan menyentuh lantai. Angkat panggul perlahan-lahan sambil mengangkat kedua tangan ke atas hingga posisi berdiri. Lakukan 8x. Posisi seperti merangkak. Lengan dibuka sejajar dengan kaki dan bahu. Tundukkan kepala sambil menarik nafas, angkatlah punggung sambil mengencangkan otot panggul. Tahan beberapa detik, lalu kembali ke posisi semula. Lakukan 8x.

Memutar Pinggang (Gb. 9,10)

Duduk dengan posisi kaki membuka, tangan dibelakang sambil menundukkan kepala. Kemudian bawa badan ke samping, ke depan, lalu serong dengan gerakan memutar pinggang.

Mengecilkan Perut (Gb. 14, 15, 16)

Mengangkat salah satu kaki bersamaan dengan mengangkat kepala dan bahu sambil tangan meraih kaki yang diangkat. Posisi terlentang dengan kaki ditekuk, tangan didada. Angkat kepala hingga bahu sambil mengencangkan perut. Lakukan gerakan ini berulang-ulang. Lanjutkan dengan gerakan mengangkat kepala dan punggung sampai posisi duduk, turunkan perlahan-lahan. Posisi tidur terlentang, angkat salah satu kaki 90 derajat, turunkan. Lakukan secara bergantian, lanjutkan dengan mengangkat kedua kaki, tahan, dan kembali ke posisi sejajar, terlentang.

Pendinginan (Gb. 17, 18, 19)

Posisi terlentang. Rentangkan kedua tangan ke atas sambil mengatur nafas. Tekuk kaki kemudian tahan dengan kedua tangan, lepaskan. Masih tidur terlentang, tekuk kaki sambil memiringkan badan, letakkan kaki ke sisi lain. Lakukan bergantian dengan kaki lainnya. Prinsip dalam melakukan pernafasan, perut dikunci hingga pada waktu bernafas perut tidak ikut bernafas. Hanya rongga dada yang bergerak.

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