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Review

Steroid profiling in pregnancy: A focus on the human fetus

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ABSTRACT

In this review we focused on steroid metabolomics in human fetuses and newborns and its role in the physiology and pathophysiology of human pregnancy and subsequent stages of human life, and on the physiological relevance of steroids influencing the nervous systems with regards to their concentrations in the fetus. Steroid profiling provides valuable data for the diagnostics of diseases related to altered steroidogenesis in the fetal and maternal compartments and placenta. We outlined a potential use of steroid metabolomics for the prediction of reproductive disorders, misbalance of hypothalamic–pituitary–adrenal axis, and impaired insulin sensitivity in subsequent stages of human life. A possible role of steroids exhibiting a non-genomic effect in the development of gestational diabetes and in the neuroprotection via negative modulation of AMPA/kainate receptors was also indicated. Increasing progesterone synthesis and catabolism, declining production of tocolytic 5β-pregnane steroids, and rising activities of steroid sulfotransferases with the approaching term may be of importance in sustaining pregnancy. An increasing trend was demonstrated with advancing gestation toward the production of ketones (and 3β-hydroxyl groups in the case of 3α-hydroxy-steroids) was demonstrated in the fetus on the expense of 3α-hydroxy-, 17β-hydroxy-, and 20α-hydroxy-groups weakening in the sequence C17, C3, and C20. There was higher production of active progestogen but lower production of active estrogen and GABAergic steroids with the approaching term. Rising activities of placental CYP19A1 and oxidative isoforms of HSD17B, and of fetal CYP3A7 with advancing gestation may protect the fetus from hyperestrogenization.

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Contents

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1. Introduction

Steroid metabolomics represents an effective tool in the physiology and pathophysiology of human pregnancy. Besides the diagnostics of numerous fetal, newborn and maternal pathologies, including preterm labor [1,2], there is a growing number of evidence that the multicomponent analysis of steroids in umbilical cord blood at labor may also be effective for predicting endocrine diseases during the lifespan [3–11]. Steroid metabolomics could be of particular importance for the diagnostics and prediction of multifactorial disorders with a polygenic background. The steroid metabolism in pregnancy (Fig. 1) was thoroughly reviewed by Pasqualini [12], the tissue distribution of corresponding enzymes was a subject of our recent review [13] and the physiological importance of sex steroids and corticoids in pregnancy is widely known, while the physiological and pathophysiological relevance of steroids influencing the fetal central and peripheral neuronal system mostly remains an open question. Therefore, we concentrated on steroids exhibiting non-genomic effects as regards their concentrations in fetal body fluids and tissues.

Besides the data found in the literature (including our own), we discuss our current unpublished results (Tables 1–4) obtained from the study group that was described in detail in our recent report [2]. The only modification was the inclusion of 30 additional women with uncomplicated pregnancies. In brief, 80 women (21–41 years of age) at labor from the week 28 to 41 of gestation participated in the study. The women were divided into three groups according to gestational age (GA) at labor. Group A, B, and C contained women

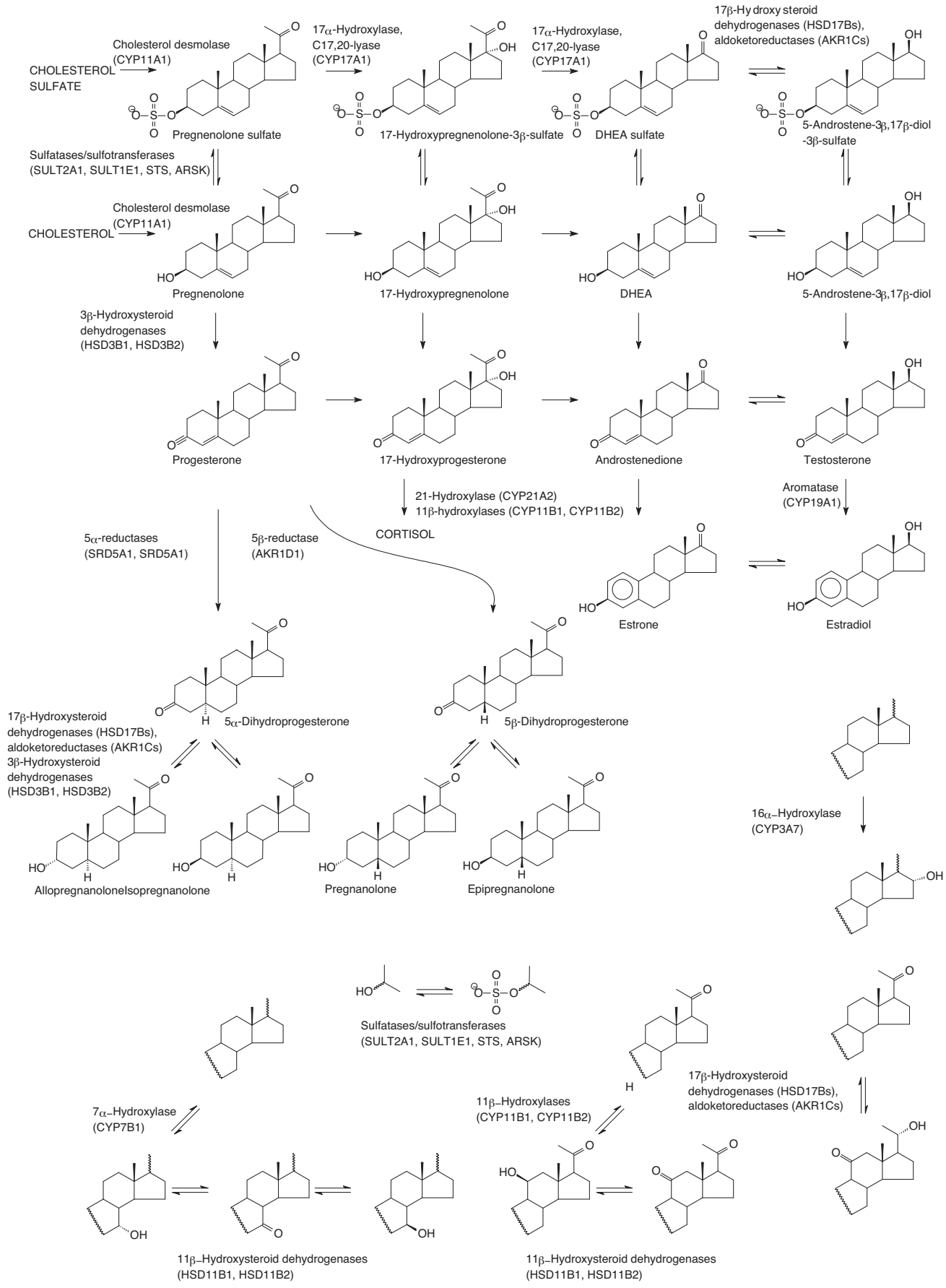

Fig. 1. Simplified scheme of steroid metabolism.

Table 1
Steroid levels in fetal umbilical arterial and venous blood at preterm and term deliveries expressed as median (quartiles), unpublished data.[a]

Steroid			GA at labor			Differences[b], dependence on GA	
			Week 28–32 (A)	Week 33–37 (B)	Week 38–42 (C)		
Pregnenolone (U)[**,a]	UA	nM	18.5 (16.7, 27.1)	19.8 (16.9, 23)	29.1 (21.1, 35.8)	A < C[*], B < C[*]	↗
Pregnenolone (U)[**]	UV≈	nM	16.8 (15.3, 24.2)[*,c]	21.3 (18.4, 30.8)	30.3 (23.8, 37.9)[*]	A < C[***]	↗
Pregnenolone (C)[***]	UA	μM	0.575 (0.341, 1.06)	1.97 (0.922, 3.38)	2.72 (2.1, 3.56)	A < B[**], A < C[***]	↗
Pregnenolone (C)[***]	UV[***,c]↓	μM	0.647 (0.364, 0.841)	1.78 (0.75, 3.49)[**]	2.39 (1.69, 2.93)[**]	A < B[**], A < C[***]	↗
17-Hydroxypregnenolone (U)	UA	nM	20.7 (11.3, 39.6)	14.4 (9.64, 29.3)	27.8 (17.5, 45.6)		~
17-Hydroxypregnenolone (U)	UV[***]↓	nM	9.24 (5.06, 18.4)[***]	9.62 (4.6, 12.3)[**]	7.21 (4.74, 10.6)[***]		~
17-Hydroxypregnenolone (C)[***]	UA	nM	60 (43.4, 169)	913 (466, 1180)	469 (222, 934)	A < B[***], A < C[***]	↗
17-Hydroxypregnenolone (C)[***]	UV≈	nM	61.6 (41.6, 117)	798 (379, 1260)	478 (224, 769)	A < B[***], A < C[***]	↗
20α-Dihydropregnenolone (U)	UA	nM	1.97 (1.38, 2.55)	2.42 (1.96, 3.06)	2.48 (1.61, 3.03)		~
20α-Dihydropregnenolone (U)[*]	UV[***]↓	nM	1.1 (0.892, 1.67)[**]	1.74 (1.28, 3.07)	1.76 (1.33, 2.32)[***]	A < B[*]	↗
20α-Dihydropregnenolone (C)[***]	UA	μM	0.447 (0.289, 1.1)	1.37 (0.882, 1.9)	1.6 (1.11, 2.07)	A < B[*], A < C[***]	↗
20α-Dihydropregnenolone (C)[***]	UV≈	μM	0.382 (0.269, 0.627)	1.48 (0.842, 1.89)	1.65 (1.19, 2.27)[*]	A < B[***], A < C[***]	↗
16α-Hydroxypregnenolone (U)[*]	UA	nM	8.04 (6.22, 11.9)	9.54 (5.64, 11.8)	10.8 (8.3, 19.1)		~
16α-Hydroxypregnenolone (U)[***]	UV[***]↓	nM	1.83 (1.6, 2.26)[***]	2.51 (1.71, 3.96)[***]	3.68 (2.74, 5.57)[***]	A < C[***]	↗
16α-Hydroxypregnenolone (C)[***]	UA	nM	1.77 (1.38, 3.16)	6.88 (4.01, 15.1)	10.3 (6.03, 15.4)	A < B[*], A < C[***]	↗
16α-Hydroxypregnenolone (C)[***]	UV≈	nM	2.29 (1.59, 5.18)	7.09 (3.43, 13.1)	8.53 (5.86, 14.2)	A < B[*], A < C[***]	↗
Dehydroepiandrosterone (U)	UA	nM	7.63 (4.41, 10.1)	7.82 (3.68, 12.6)	9.85 (5.82, 15.6)		~
Dehydroepiandrosterone (U)[*]	UV[***]↓	nM	1.57 (1.03, 2.64)[***]	2.07 (1.46, 3.35)[**]	2.6 (1.88, 3.84)[***]	A < C[*]	↗
Dehydroepiandrosterone (C)[***]	UA	μM	0.569 (0.185, 0.791)	1.63 (0.702, 2.34)	1.51 (1.15, 2.53)	A < B[**], A < C[***]	↗
Dehydroepiandrosterone (C)[***]	UV[*]↓	μM	0.547 (0.307, 0.966)[*]	1.6 (0.728, 2.15)	1.48 (0.917, 2.12)[*]	A < B[**], A < C[***]	↗
16α-Hydroxy-DHEA (U)[***,a]	UA	nM	1.95 (0.863, 3.89)	2.52 (2.17, 3.77)	7.1 (3.79, 20.1)	A < C[***], B < C[***]	~
16α-Hydroxy-DHEA (U)[***]	UV[***,c]↑	nM	4.45 (2.47, 5.26)[***,c]	5.8 (4.2, 7.41)[***]	24.8 (11.4, 52.7)[***]	A < C[***], B < C[***]	↗
16α-Hydroxy-DHEA (C)	UA	μM	0.603 (0.079, 1.24)	0.549 (0.208, 1.28)	1.06 (0.281, 1.92)		↗
16α-Hydroxy-DHEA (C)[**]	UV[***]↑	μM	0.766 (0.39, 1.07)	0.655 (0.389, 1.83)[*]	2.35 (0.905, 4.67)[**]	A < C[**], B < C[*]	↗
7α-Hydroxy-DHEA (U)	UA	nM	1.41 (1.03, 1.9)	1.55 (1.16, 2.09)	1.91 (1.45, 2.41)		~
7α-Hydroxy-DHEA (U)[***]	UV[***]↓	nM	1.02 (0.645, 1.5)[**]	1 (0.681, 1.37)[*]	1.52 (1.12, 2.18)	A < C[**], B < C[*]	↗
7β-Hydroxy-DHEA (U)[**]	UA	nM	0.185 (0.080, 0.343)	0.156 (0.125, 0.221)	0.276 (0.21, 0.347)	A < C[*], B < C[*]	↗
7β-Hydroxy-DHEA (U)[***]	UV[***]↓	nM	0.111 (0.032, 0.14)[**]	0.132 (0.084, 0.254)	0.218 (0.18, 0.271)[***]	A < C[***]	↗
Androstenediol (U)[**]	UA	pM	472 (409, 747)	363 (222, 469)	301 (184, 407)	A > C[**]	↘
Androstenediol (U)[**]	UV[***]↓	pM	240 (92, 352)[**]	146 (81.3, 279)[**]	96.9 (76.8, 137)[***]	A > C[**]	↘
Androstenediol (C)[***]	UA	μM	0.185 (0.149, 0.341)	1.33 (0.715, 2.84)	2.61 (1.73, 3.78)	A < B[***], A < C[***]	↗
Androstenediol (C)[***]	UV[**]↑	μM	0.196 (0.147, 0.377)[**]	0.992 (0.718, 3.09)	2.66 (1.72, 4.1)[***]	A < B[***], A < C[***]	↗
5-Androstene-3β,7α,17β-triol (U)[***]	UA	pM	8.92 (6.13, 19.4)	17.4 (12.7, 28.5)	25.6 (16.4, 46.3)	A < C[***]	↗
5-Androstene-3β,7α,17β-triol (U)[**]	UV[***]↓	pM	2.93 (1.29, 5.19)[**]	4.14 (3.14, 9.67)[**]	6.21 (3.67, 11.1)[***]	A < C[**]	↗
5-Androstene-3β,7α,17β-triol (C)[***]	UA	pM	50.7 (15.3, 84)	353 (239, 637)	504 (380, 799)	A < B[***], A < C[***]	↗
5-Androstene-3β,7α,17β-triol (C)[***]	UV[*]↓	pM	45.9 (15.8, 89.2)	287 (145, 625)	474 (285, 662)[*]	A < B[***], A < C[***]	↗
5-Androstene-3β,7β,17β-triol (U)[*]	UA	pM	9.18 (5.55, 16.9)	10.4 (7.65, 13)	15.4 (8.93, 28.2)	A < C[*]	↗
5-Androstene-3β,7β,17β-triol (U)[**]	UV[***]↓	pM	3.27 (2.29, 6.84)[**]	6.34 (4.45, 10.5)	7.28 (5.41, 11.5)[***]	A < C[**]	↗
5-Androstene-3β,7β,17β-triol (C)[***]	UA	pM	23.9 (16.1, 59.8)	179 (107, 374)	600 (421, 993)	A < B[*], A < C[***], B < C[***]	↗
5-Androstene-3β,7β,17β-triol (C)[***]	UV[**]↓	pM	33 (16.8, 56)	129 (88.7, 352)	484 (279, 760)[*]	A < B[*], A < C[***], B < C[**]	↗
Progesterone[**]	UA	μM	0.71 (0.404, 0.964)	0.51 (0.39, 0.622)	0.824 (0.533, 1.07)	B < C[**]	↗
Progesterone[**]	UV[***]↑	μM	0.946 (0.811, 1.57)[**]	1.08 (0.861, 1.23)[***]	1.44 (1, 2.1)[***]	B < C[*]	↗
17-Hydroxyprogesterone (U)[***]	UA	nM	27.1 (14.4, 33)	23.1 (18.2, 36.1)	52.2 (44, 73.1)	A < C[***], B < C[***]	↗
17-Hydroxyprogesterone (U)[***]	UV[***]↑	nM	29.6 (20.7, 42.6)[*]	47.4 (35.7, 58.4)[***]	74.9 (50.9, 100)[**]	A < C[***], B < C[*]	↗
17-Hydroxyprogesterone (C)[*]	UA	nM	9.34 (9.32, 42.5)	33.9 (22.1, 38.7)	47.1 (42.2, 57)	A < C[*]	↗
17-Hydroxyprogesterone (C)[***]	UV≈	nM	16.1 (12, 21.2)	27.5 (14.6, 37.1)	48.2 (38.8, 60.4)	A < C[***], B < C[*]	↗
20α-Dihydroprogesterone (U)	UA	nM	91.7 (57.2, 118)	82.9 (66.8, 156)	88.1 (60.9, 123)		~
20α-Dihydroprogesterone (U)	UV[***]↓	nM	44.7 (32.2, 71.7)[***]	64 (37.8, 121)[*]	52.8 (36.2, 85.8)[***]		~
20α-Dihydroprogesterone (C)[***]	UA	nM	47.9 (29.1, 83.4)	84.1 (50.7, 118)	99.4 (77.8, 153)	A < C[***]	↗
20α-Dihydroprogesterone (C)[***]	UV≈	nM	44.1 (32.5, 93.9)	102 (81.7, 164)[*]	101 (80, 161)	A < B[**], A < C[***]	↗
16α-Hydroxyprogesterone (U)[***]	UA	nM	53.5 (36.9, 82.8)	76.7 (40.6, 102)	163 (103, 234)	A < C[***], B < C[***]	↗
16α-Hydroxyprogesterone (U)[***]	UV[***]↑	nM	78.5 (45.3, 110)[**]	105 (67.4, 182)[***]	273 (176, 411)[***]	A < C[***], B < C[***]	↗
Estrone (U)[***]	UA	nM	2.34 (1.61, 3.15)	4.64 (3.13, 8.92)	13.6 (7.55, 23.6)	A < B[*], A < C[***], B < C[**]	↗
Estrone (U)[***]	UV[***]↑	nM	16.6 (10.6, 20.8)[***]	27.9 (17.2, 56.6)[***]	72.3 (45.1, 127)[***]	A < C[***], B < C[**]	↗
Estrone (C)[***]	UA	nM	39.1 (19.5, 62.4)	191 (107, 231)	122 (87.7, 217)	A < B[***], A < C[***]	↗
Estrone (C)[***]	UV[*]↓	nM	25.7 (17.7, 47.5)	138 (98.7, 199)	106 (82.9, 209)[*]	A < B[***], A < C[***]	↗
16α-Hydroxyestrone (U)[***]	UA	nM	0.168 (0.067, 0.554)	0.533 (0.376, 0.722)	1.62 (1.35, 2.27)	A < C[***], B < C[**]	↗
16α-Hydroxyestrone (U)[***]	UV[***]↑	nM	1.72 (1.33, 2.09)[***]	2.03 (1.39, 3.1)[***]	8.9 (6.27, 9.74)[***]	A < C[***], B < C[**]	↗
Estradiol (U)[***]	UA	nM	0.915 (0.748, 1.38)	1.66 (1.02, 2.74)	3.05 (1.92, 6.17)	A < C[***], B < C[*]	↗
Estradiol (U)[***]	UV[***]↑	nM	3.64 (2.61, 5.24)[***]	8.26 (3.41, 10.4)[***]	12.5 (6.62, 17.7)[***]	A < C[***]	↗
Estradiol (C)[***]	UA	nM	11.9 (8.91, 15.5)	26.4 (16.2, 34.6)	13.3 (8.3, 17.1)	A < B[***], B > C[***]	∩
Estradiol (C)[***]	UV≈	nM	8.82 (6.87, 12.6)	22.8 (17.8, 30.8)	14.5 (9.45, 19.4)[***]	A < B[***], A < C[*], B > C[**]	∩
Estriol (U)[***]	UA	nM	11.8 (6.68, 18.4)	21.2 (11.6, 39)	49 (34, 75.4)	A < C[***], B < C[**]	↗
Estriol (U)[***]	UV[***]↑	nM	70.4 (52.7, 107)[***]	103 (77, 168)[***]	216 (145, 308)[***]	A < C[***], B < C[**]	↗
Estriol (C)[***]	UA	μM	1.04 (0.602, 1.25)	3.94 (3.23, 5.1)	2.87 (2.35, 3.94)	A < B[***], A < C[***]	↗
Estriol (C)[***]	UV[***]↓	μM	0.676 (0.48, 1.01)[***]	3.55 (2.56, 4.63)	2.78 (2.09, 3.46)[*]	A < B[***], A < C[***]	↗
Androstenedione[***]	UA	nM	2.59 (0.984, 3.13)	1.32 (0.761, 2.27)	3.55 (2.67, 4.46)	A < C[**], B < C[***]	↗
Androstenedione[***]	UV[***]↓	nM	1.05 (0.6, 1.61)[***]	1.11 (0.676, 1.92)	2.03 (1.7, 2.6)[***]	A < C[***], B < C[**]	↗
16α-Hydroxyandrostenedione (U)[***]	UA	nM	2.47 (0.796, 3.08)	2.73 (1.61, 3.3)	11 (4.23, 18)	A < C[***], B < C[***]	↗
16α-Hydroxyandrostenedione (U)[***]	UV≈	nM	2.48 (1.71, 3.66)[*]	2.86 (1.59, 3.27)	9.71 (5.29, 15.1)	A < C[***], B < C[***]	↗
Testosterone (U)[**]	UA	nM	4.02 (1.39, 6.99)	1.04 (0.687, 2.24)	1.32 (0.751, 1.78)	A > B[*], A > C[**]	↘
Testosterone (U)	UV[**]↓	nM	1.61 (0.746, 3.06)[***]	0.915 (0.722, 1.26)	1.36 (0.893, 1.74)		~

Table 1 (*Continued*)

Steroid			GA at labor			Differences[b], dependence on GA	
			Week 28–32 (A)	Week 33–37 (B)	Week 38–42 (C)		
16α-Hydroxytestosterone (U)***	UA	nM	6.54 (3.34, 12.2)	7.05 (4.96, 9.25)	13.6 (9.01, 22.5)	A < C***, B < C***	↗
16α-Hydroxytestosterone (U)***	UV≈	nM	3.12 (2.76, 8.65)*	5.49 (3.93, 11.8)	11.9 (9.35, 18.7)	A < C***, B < C**	↗
Androsterone (U)	UA	pM	139 (111, 191)	179 (91.3, 220)	158 (97.2, 213)		~
Androsterone (U)	UV*** ↓	pM	69.8 (41.9, 131)***	80.5 (61.1, 122)*	59.8 (41.1, 89.1)***		~
Androsterone (C)***	UA	nM	4.82 (2.5, 8.13)	14.8 (8.93, 20.4)	13.9 (10.9, 19.1)	A < B**, A < C***	↗
Androsterone (C)***	UV≈	nM	5.81 (3.5, 9.93)**	16.6 (11.2, 18.4)	14 (9.27, 19.1)	A < B**, A < C**	↗
Epiandrosterone (C)**	UA	nM	24.9 (6.63, 39)	49.7 (22.6, 65.8)	52.9 (41.4, 90.3)	A < C**	↗
Epiandrosterone (C)***	UV* ↓	nM	22.9 (12.3, 31.4)	43.1 (24.8, 101)	52 (31.6, 79.2)*	A < B*, A < C***	↗
Etiocholanolone (U)	UA	pM	50.4 (36.7, 63.8)	38.3 (28.2, 48.9)	56.7 (27.8, 74)		~
Etiocholanolone (U)	UV≈	pM	46.5 (26.8, 74.5)	35.5 (24.8, 61.9)	50.1 (34.5, 71.6)		~
Etiocholanolone (C)*	UA	nM	0.77 (0.578, 2.41)	2.96 (1.28, 4.02)	2.58 (1.5, 3.57)	A < C*	↗
Etiocholanolone (C)	UV* ↑	nM	1.37 (0.861, 2.46)**	2.99 (1.39, 4.42)	2.53 (1.34, 3.4)		~
5α-Androstane-3α,17β-diol (C)***	UA	nM	5.94 (3.66, 8.31)	25 (17.4, 37.7)	13.6 (8.34, 17.5)	A < B***, A < C**, B > C**	∩
5α-Androstane-3α,17β-diol (C)***	UV* ↑	nM	6.24 (4.15, 9.6)*	22.1 (17.3, 45.5)	13.5 (9.79, 18.5)*	A < B***, A < C**, B > C**	∩
5α-Androstane-3β,17β-diol (C)***	UA	nM	2.27 (1.48, 3.73)	7.97 (5.84, 10.9)	4.37 (2.77, 8.05)	A < B***, A < C*, B > C*	∩
5α-Androstane-3β,17β-diol (C)***	UV≈	nM	2.33 (1.4, 4.42)	8.23 (5.07, 13)	5.84 (3.06, 7.98)	A < B***, A < C**	↗
5β-Androstane-3α,17β-diol (C)***	UA	nM	1.81 (1.45, 2.4)	5.72 (2.28, 10.4)	3.83 (3.08, 4.73)	A < B***, A < C***	↗
5β-Androstane-3α,17β-diol (C)***	UV≈	nM	1.8 (1.4, 2.18)	5.05 (3.17, 11.2)	3.86 (2.66, 5.15)	A < B***, A < C***	↗
5α-Dihydroprogesterone***	UA	nM	31.9 (21.5, 50.6)	23.6 (16.7, 34.2)	45.1 (29.2, 59.7)	B < C***	↗
5α-Dihydroprogesterone	UV≈	nM	35.9 (17.7, 45.8)	28.8 (21.5, 36)	36.9 (28.5, 58.6)		~
Allopregnanolone (U)	UA	nM	6.44 (4.14, 10)	4.93 (3.98, 6.38)	4.93 (3.61, 7.19)		~
Allopregnanolone (U)	UV≈	nM	5.51 (4.28, 7.24)	5.79 (5.26, 6.81)	4.44 (3.15, 6)*		~
Allopregnanolone (C)***	UA	nM	123 (69.4, 184)	421 (322, 671)	230 (179, 414)	A < B***, A < C**, B > C*	∩
Allopregnanolone (C)***	UV*** ↑	nM	144 (92.6, 225)***	562 (406, 927)**	287 (224, 442)***	A < B***, A < C**, B > C*	∩
Isopregnanolone (U)	UA	nM	11.6 (7.34, 17.5)	9.03 (6.66, 11.8)	9.71 (8.21, 13.7)		~
Isopregnanolone (U)	UV*** ↓	nM	6.69 (4.53, 8.7)***	6.84 (4.78, 10)*	6.74 (4.28, 10.5)***		~
Isopregnanolone (C)***	UA	nM	85.4 (56, 164)	289 (135, 482)	339 (255, 433)	A < B***, A < C***	↗
Isopregnanolone (C)***	UV≈	nM	81.1 (57.8, 198)	324 (167, 530)	302 (247, 464)	A < B***, A < C***	↗
5β-Dihydroprogesterone*	UA	nM	13.7 (8.81, 19.5)	7.4 (4.98, 10.2)	8.66 (5.81, 13.1)	A > B*	↘
5β-Dihydroprogesterone*	UV** ↓	nM	12.3 (8.34, 16.9)	6.4 (5.32, 7.72)	7.38 (4.61, 12.1)**	A > B*	↘
Pregnanolone (U)**	UA	nM	16.7 (12.6, 21.8)	12 (8.4, 13.6)	10.3 (7.04, 14.9)	A > B*, A > C**	↘
Pregnanolone (U)*	UV*** ↓	nM	7.19 (4.6, 9.46)***	5.21 (4.12, 7.67)***	4.49 (2.91, 6.32)***	A > C*	↘
Pregnanolone (C)***	UA	nM	96.4 (67.6, 110)	259 (165, 355)	178 (144, 253)	A < B***, A < C***	↗
Pregnanolone (C)***	UV≈	nM	94.5 (67.7, 128)*	265 (176, 365)	187 (142, 238)	A < B***, A < C***	↗
Epipregnanolone (U)***	UA	nM	2.17 (1.39, 2.93)	1.35 (1.05, 1.67)	0.983 (0.699, 1.39)	A > C***	↘
Epipregnanolone (U)*	UV*** ↓	nM	1.32 (0.699, 1.43)***	0.739 (0.562, 1.12)***	0.611 (0.418, 1.02)***	A > C*	↘
Epipregnanolone (C)***	UA	nM	33.8 (21.5, 50.5)	67.7 (44.8, 112)	48.4 (39.8, 66.1)	A < B***, A < C*	↗
Epipregnanolone (C)***	UV*** ↑	nM	40.8 (22.5, 57.6)**	91 (57.6, 154)**	61.5 (46.3, 77.3)**	A < B***, A < C*	↗
5α,20α-Tetrahydroprogesterone (U)	UA	nM	76.3 (58.1, 85.5)	60.6 (50.3, 102)	62.7 (41, 92.1)		~
5α,20α-Tetrahydroprogesterone (U)	UV*** ↓	nM	47.4 (40.4, 60.8)***	66.7 (42.1, 81.9)	47.1 (33.1, 66.1)***		~
5α,20α-Tetrahydroprogesterone (C)***	UA	nM	70.7 (55.5, 118)	197 (171, 307)	122 (74.2, 181)	A < B***, A < C*, B > C*	∩
5α,20α-Tetrahydroprogesterone (C)***	UV≈	nM	79.1 (67.4, 119)*	215 (166, 314)	119 (90, 157)	A < B***, B > C**	∩
5α-Pregnane-3α,20α-diol (U)	UA	nM	3.15 (1.81, 6.87)	2.73 (2.05, 3.13)	2.94 (2.57, 6.09)		~
5α-Pregnane-3α,20α-diol (U)	UV*** ↓	nM	1.74 (1.14, 4.36)***	1.96 (1.43, 2.52)*	2.05 (1.4, 2.62)***		~
5α-Pregnane-3α,20α-diol (C)***,[a]	UA	nM	776 (426, 1160)	2790 (1830, 3690)	949 (706, 1470)	A < B***, B > C***	∩
5α-Pregnane-3α,20α-diol (C)***	UV***,[c] ↑	nM	898 (575, 1360)***,[c]	2740 (1820, 4220)	1120 (804, 1530)***	A < B***, B > C***	∩
5α-Pregnane-3β,20α-diol (U)	UA	nM	2.71 (2.12, 3.4)	2.31 (1.81, 3.16)	2.43 (1.78, 3.56)		~
5α-Pregnane-3β,20α-diol (U)	UV≈	nM	2.1 (1.8, 2.62)**	2.45 (1.85, 3.48)	2.03 (1.45, 4.03)		~
5α-Pregnane-3β,20α-diol (C)***	UA	μM	0.919 (0.4, 1.35)	2.79 (1.72, 4.64)	1.78 (1.21, 2.26)	A < B***, A < C**	↗
5α-Pregnane-3β,20α-diol (C)***	UV*** ↑	μM	0.966 (0.574, 1.33)*	3.18 (2.34, 4.89)	1.78 (1.39, 2.5)**	A < B***, A < C**, B > C*	∩
5β,20α-Tetrahydroprogesterone (U)*	UA	nM	27.9 (18.2, 41.6)	20.8 (16.8, 26.7)	14.8 (9.38, 28.7)	A > C*	↘
5β,20α-Tetrahydroprogesterone (U)*	UV*** ↓	nM	20.6 (12.5, 32.1)**	17.4 (14.6, 24.6)*	11.8 (8.02, 21)***	A > C*	↘
5β,20α-Tetrahydroprogesterone (C)	UA	nM	40.7 (25.4, 74.7)	66.9 (45.2, 77.4)	45.6 (34.6, 80.9)		~
5β,20α-Tetrahydroprogesterone (C)	UV≈	nM	35.9 (26.9, 79.4)	56.2 (33.9, 88.2)	51.8 (37.4, 77.7)		~
5β-Pregnane-3α,20α-diol (U)***	UA	nM	25.6 (18.3, 34.6)	17.4 (12, 18.8)	12.4 (9.4, 15.3)	A > B*, A > C***	↘
5β-Pregnane-3α,20α-diol (U)***	UV*** ↓	nM	7.18 (4.4, 9.99)***	6.38 (4.18, 8.21)***	3.24 (2.45, 4.81)***	A > C***, B > C**	↘
5β-Pregnane-3α,20α-diol (C)***	UA	μM	1.02 (0.749, 1.5)	2.52 (1.81, 3.76)	1.39 (1.04, 2.25)	A < B***, B > C*	∩
5β-Pregnane-3α,20α-diol (C)***	UV≈	μM	1 (0.758, 1.3)	3.24 (2.08, 3.8)	1.13 (0.758, 1.77)	A < B***, B > C***	∩
5β-Pregnane-3β,20α-diol (U)*	UA	pM	775 (320, 964)	658 (454, 869)	419 (287, 595)		~
5β-Pregnane-3β,20α-diol (U)	UV*** ↓	pM	398 (159, 560)*	349 (264, 566)***	199 (151, 388)***		~
5β-Pregnane-3β,20α-diol (C)***	UA	nM	210 (124, 255)	449 (405, 727)	281 (202, 372)	A < B***, B > C**	∩
5β-Pregnane-3β,20α-diol (C)***	UV* ↑	nM	198 (138, 268)*	579 (421, 795)	282 (212, 399)	A < B***, B > C***	∩

[a] The sample consists of 80 women (21–41 years of age) at labor from the week 28–41 of gestation. The samples were assorted into three categories according to the GA at labor. Group A, B, and C contained women laboring within week 28–32 ($n = 19$), week 33–37 ($n = 19$), and week 38–42 ($n = 42$) of gestation. ↗: increasing trend with GA, ~: no change with GA, ↘: decreasing trend with GA, ∩: maximum in Group B; ↑: higher values in UV, ↓: lower values UV, ≈: no significant difference between UA and UV.

[b] Kruskal–Wallis test.

[c] Dunn's multiple comparisons with Bonferroni correction; Wilcoxon's paired test.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Table 2
Steroid correlations between umbilical arterial and umbilical venous blood at preterm and term deliveries, unpublished data.

Steroid	Unconjugated steroids			Steroid polar conjugates			Δr
	r	*p*	*n*	*r*	*p*	*n*	*p*
Pregnenolone	0.689	<0.001	76	0.975	<0.001	70	<0.001
17-Hydroxypregnenolone	0.711	<0.001	79	0.980	<0.001	66	<0.001
20α-Dihydropregnenolone	0.781	<0.001	74	0.982	<0.001	69	<0.001
16α-Hydroxypregnenolone	0.851	<0.001	74	0.669	<0.001	75	0.007
Dehydroepiandrosterone	0.770	<0.001	75	0.954	<0.001	72	<0.001
16α-Hydroxy-DHEA	0.846	<0.001	77	0.423	<0.001	76	<0.001
7α-Hydroxy-DHEA	0.474	<0.001	79	–	–	–	–
7β-Hydroxy-DHEA	0.652	<0.001	76	–	–	–	–
Androstenediol	0.502	<0.001	79	0.992	<0.001	74	<0.001
5-Androstene-3β,7α,17β-triol	0.422	<0.001	78	0.818	<0.001	73	<0.001
5-Androstene-3β,7β,17β-triol	0.411	<0.001	75	0.930	<0.001	73	<0.001
Progesterone	0.593	<0.001	75	–	–	–	–
17-Hydroxyprogesterone	0.865	<0.001	46	0.914	<0.001	30	0.332
20α-Dihydroprogesterone	0.853	<0.001	75	0.875	<0.001	71	0.607
16α-Hydroxyprogesterone	0.924	<0.001	78	–	–	–	–
Estrone	0.912	<0.001	75	0.931	<0.001	73	0.451
16α-Hydroxyestrone	0.740	<0.001	52	–	–	–	–
Estradiol	0.895	<0.001	73	0.870	<0.001	74	0.501
Estriol	0.809	<0.001	77	0.929	<0.001	73	0.002
Androstenedione	0.831	<0.001	73	–	–	–	–
16α-Hydroxyandrostenedione	0.833	<0.001	76	–	–	–	–
Testosterone	0.668	<0.001	77	–	–	–	–
16α-Hydroxytestosterone	0.794	<0.001	78	–	–	–	–
5α-Dihydroprogesterone	0.776	<0.001	76	–	–	–	–
Androsterone	0.501	<0.001	76	0.914	<0.001	73	<0.001
Epiandrosterone	–	–	–	0.884	<0.001	74	–
Etiocholanolone	0.379	<0.001	77	0.930	<0.001	72	<0.001
5α-Androstane-3α,17β-diol	–	–	–	0.970	<0.001	74	–
5α-Androstane-3β,17β-diol	–	–	–	0.909	<0.001	73	–
5β-Androstane-3α,17β-diol	–	–	–	0.874	<0.001	73	–
Allopregnanolone	0.704	<0.001	74	0.982	<0.001	74	<0.001
Isopregnanolone	0.803	<0.001	76	0.978	<0.001	75	<0.001
5β-Dihydroprogesterone	0.847	<0.001	74	–	–	–	–
Pregnanolone	0.733	<0.001	77	0.966	<0.001	74	<0.001
Epipregnanolone	0.755	<0.001	78	0.931	<0.001	72	<0.001
5α,20α-Tetrahydroprogesterone	0.781	<0.001	75	0.892	<0.001	72	0.023
5α-Pregnane-3α,20α-diol	0.542	<0.001	75	0.987	<0.001	74	<0.001
5α-Pregnane-3β,20α-diol	0.872	<0.001	77	0.982	<0.001	73	<0.001
5β,20α-Tetrahydroprogesterone	0.936	<0.001	74	0.864	<0.001	71	0.020
5β-Pregnane-3α,20α-diol	0.866	<0.001	75	0.974	<0.001	65	<0.001
5β-Pregnane-3β,20α-diol	0.737	<0.001	73	0.974	<0.001	73	<0.001

r: Pearson's correlation coefficient after power transformation of original data for attaining data symmetry and constant variance, *p*: statistical significance, *n*: subjects investigated, Δr: difference between correlation coefficients for unconjugated steroids and steroid polar conjugates.

laboring within week 28–32 ($n = 19$), week 33–37 ($n = 19$), and week 38–42 ($n = 42$) of gestation. The women in group C were without perinatological complications. We strove to select the women to provide maximum conformity of steroid metabolome with the actual GA.

2. Steroid levels in fetuses and neonates

2.1. Δ^5 steroids

2.1.1. Levels of Δ^5 steroids in fetal body fluids and tissues

Fetal circulation contains micromolar concentrations of conjugated Δ^5 steroids and their 16α-hydroxy-metabolites in fetal body fluids. Furthermore, anencephalic fetuses with reduced FZ have pronouncedly lower levels of the Δ^5 steroids and their 16α-hydroxy- and 20α-dihydrometabolites [14,15]. Sulfated Δ^5 steroids may also be present in high concentrations in various fetal tissues and amniotic fluid (AF). For instance, the levels of pregnenolone and pregnenolone sulfate (PregS) in fetal tissues and AF displayed as mean (maximum) are as follows (pmol/g): PregS: brain 38 (124), placenta 0 (0), AF 92 (111), skin 166 (347), lung 420 (688), liver 325 (828), kidney 682 (2178), intestine 739 (2013), myometrium 41 (455); Pregnenolone: brain 29 (61), placenta 64 (86), AF 0 (3), skin 452 (975), lung 433 (1873), liver 29 (118), kidney 315 (732), intestine 140 (1178), myometrium 33 (280) [16–18].

While the levels of sulfated C21 Δ^5 steroids and sulfated androstenediol are strikingly higher in the fetal circulation than in the circulation of non-pregnant women [19,20], those of sulfated dehydroepiandrosterone (DHEAS) are about twice as lower than in non-pregnant women [13,21,22] (Table 1). The concentrations of unconjugated Δ^5 steroids in umbilical blood are about 1.3–20 times higher as compared to the situation in non-pregnant women in the follicular menstrual phase [13,19–21,23,24].

The excessively elevated levels of sulfated androstenediol in fetal blood indicate markedly elevated activity of reductive isoforms of HSD17Bs and AKR1C1 in the fetus when compared to the situation in non-pregnant subjects, which prompts speculation of whether the overproduction of sulfated androstenediol in the fetus is associated with a more efficient pathway for placental production of estrogens, which functions concurrently with that employing the fetal DHEAS as the primary substrate.

Various data (including our own [2,13,14,24–31] and our current unpublished data (Table 1)) demonstrate a key role of the fetal zone

Table 3
Relationships between gestational age at deliveries and steroid ratios in umbilical blood related to activities of individual steroidogenic enzymes, unpublished data.

Enzyme		Steroid ratio	Gestational age at labor			Differences, dependence on GA	
			Week 28–32 (A)	Week 33–37 (B)	Week 38–42 (C)		
CYP17A1	UA	17-Hydroxpregnenolone/pregnenolone* (C)	0.137 (0.0677, 0.466)	0.377 (0.281, 0.502)	0.181 (0.0963, 0.309)	A < B*, B > C*	⊂
	UV≈	17-Hydroxpregnenolone/pregnenolone* (C)	0.0884 (0.0693, 0.293)	0.424 (0.265, 0.633)	0.208 (0.122, 0.356) **	A < B*	↗
	UA	DHEA/17-Hydroxpregnenolone (C)	3.34 (1.58, 14.3)	1.77 (1.01, 3.86)	3.03 (2.1, 6.44)		~
	UV≈	DHEA/17-Hydroxpregnenolone* (C)	7.64 (3.23, 16.8) *	1.24 (1.18, 5)	2.45 (1.49, 5.04) **	A > B*	↘
HSD3Bs ~ or ↗	UA	Progesterone/pregnenolone	30.7 (23.6, 44.1)	25 (18.8, 31.5)	31.1 (22.3, 44.2)		~
	UV***,c↑	Progesterone/pregnenolone	54.2 (49, 68.8)**	47.8 (31.2, 56.7)***	50 (38.5, 59.3)***		~
	UA	17-Hydroxyprogesterone/17-hydroxypregnenolone	1.34 (0.934, 2.34)	1.78 (0.587, 2.66)	2.4 (1.35, 3.75)		~
	UV***↑	17-Hydroxyprogesterone/17-hydroxypregnenolone***	3.45 (2.08, 5.8)**	6.28 (3.92, 10.8)***	11.1 (8.9, 12.8)***	A < C***	↗
	UA	Androstenedione/DHEA**	0.226 (0.172, 0.356)	0.189 (0.14, 0.254)	0.369 (0.218, 0.522)	B < C**	↗
	UV***↑	Androstenedione/DHEA*	0.615 (0.48, 0.79)***	0.498 (0.411, 0.727)***	0.819 (0.549, 1.17)***	B < C*	↗
	UA	Testosterone/androstenediol	8.21 (3.29, 14.1)	3 (2.64, 7.2)	4.47 (2.18, 8.05)		~
	UV***↑	Testosterone/androstenediol	5.87 (3.36, 17)	7.52 (4.54, 12) **	13.8 (6.73, 20.3)***		~
CYP19A1 ↗	UA	Estrone/androstenedione***	1.05 (0.694, 2.49)	3.68 (2.74, 8.49)	3.37 (2.08, 7.79)	A < B**, A < C***	↗
	UV***↑	Estrone/androstenedione**	17.1 (8.84, 23)***	27.2 (16.7, 45.7)***	32.7 (21.2, 51.3)***	A < C***	↗
	UA	Estradiol/testosterone***	0.295 (0.161, 0.493)	1.52 (0.934, 1.89)	3.34 (1.14, 5.98)	A < B**, A < C***	↗
	UV***↑	Estradiol/testosterone***	1.88 (1.11, 3.24)***	5.75 (4.57, 11.5)***	10.8 (7.25, 15.7)***	A < B**, A < C***	↗
	UA	16α-Hydroxypregnenolone/pregnenolone	0.424 (0.314, 0.528)	0.457 (0.355, 0.505)	0.453 (0.338, 0.64)		~
	UV***↓	16α-Hydroxypregnenolone/pregnenolone	0.104 (0.0894, 0.124)***	0.134 (0.0946, 0.149)***	0.112 (0.0791, 0.178)***		~
	UA	16α-Hydroxyprogesterone/progesterone***	0.0859 (0.0597, 0.178)	0.154 (0.0949, 0.182)	0.204 (0.129, 0.26)	A < C***	↗
	UV***↓	16α-Hydroxyprogesterone/progesterone***	0.0697 (0.0507, 0.115) *	0.126 (0.0714, 0.182) *	0.162 (0.119, 0.274)	A < C***	↗
	UA	16α-Hydroxy-DHEA/DHEA*	0.298 (0.122, 0.536)	0.364 (0.28, 0.71)	0.777 (0.276, 2.49)	A < C*	↗
	UV***↑	16α-Hydroxy-DHEA/DHEA***	3.02 (1.96, 4.01)***	3.42 (1.87, 3.6)***	7.81 (3.81, 23.7)***	A < C***, B < C**	↗
CYP3A7 ↗	UA	16α-Androstenedione/androstenedione**	0.892 (0.347, 1.4)	2.23 (1.31, 3.04)	3.2 (1.51, 5.41)	A < C***	↗
	UV***↑	16α-Androstenedione/androstenedione*	2.91 (1.64, 4.85)**	2.34 (1.39, 4.39)	4.98 (2.09, 7.61) **		~
	UA	16α-Hydroxytestosterone/testosterone***	1.97 (1.21, 3.83)	5.12 (3.3, 8.09)	11.3 (6.95, 20.1)	A < B*, A < C***, B < C*	↗
	UV≈	16α-Hydroxytestosterone/testosterone***	3.09 (2.49, 4.6)	6.89 (2.79, 12.3)	10.9 (8.52, 19.1)	A < C***, B < C*	↗
	UA	16α-Hydroxyestrone/estrone	0.080 (0.036, 0.176)	0.091 (0.053, 0.124)	0.106 (0.0615, 0.169)		~
	UV≈	16α-Hydroxyestrone/estrone	0.115 (0.079, 0.177)	0.084 (0.050, 0.109)	0.073 (0.059, 0.138) *		~
	UA	Estriol/estradiol	12.1 (7.51, 15)	11.8 (10.2, 22.6)	16.2 (10.5, 23.9)		~
	UV**↑	Estriol/estradiol	21.6 (11.8, 44) **	15.6 (9.48, 27.8)	17.3 (12.8, 26.4)		~
SRD5As ~	UA	5α-Dihydroprogesterone/progesterone	0.052 (0.039, 0.056)	0.043 (0.036, 0.058)	0.057 (0.041, 0.073)		~
	UV***↓	5α-Dihydroprogesterone/progesterone	0.0267 (0.0211, 0.0354)**	0.025 (0.021, 0.039)***	0.0275 (0.0187, 0.0348)***		~
	UA	5α,20α-Tetrahydroprogesterone/20α-dihydroprogesterone	0.787 (0.733, 0.997)	0.669 (0.558, 0.778)	0.709 (0.589, 0.835)		~
	UV***↑	5α,20α-Tetrahydroprogesterone/20α-dihydroprogesterone	0.978 (0.752, 1.32) **	0.842 (0.608, 1.07) **	0.884 (0.666, 1.1)**		~
AKR1D1 ↘	UA	5β-Dihydroprogesterone/progesterone**	0.021 (0.017, 0.031)	0.016 (0.010, 0.0187)	0.012 (0.007, 0.019)	A > C**	↘
	UV***↓	5β-Dihydroprogesterone/progesterone***	0.011 (0.001 0.016)***	0.0064 (0.005, 0.010)***	0.0046 (0.0035, 0.0074)***	A > C***	↘
	UA	5β,20α-Tetrahydroprogesterone/20α-dihydroprogesterone*	0.383 (0.21, 0.465)	0.224 (0.121, 0.308)	0.15 (0.113, 0.253)	A > C*	↘
	UV***↑	5β,20α-Tetrahydroprogesterone/20α-dihydroprogesterone**	0.444 (0.251, 0.608) ***	0.3 (0.158, 0.45) **	0.205 (0.147, 0.3) ***	A > C**	↘

Table 3 (*Continued*)

Enzyme		Steroid ratio	Gestational age at labor			Differences, dependence on GA	
			Week 28–32 (A)	Week 33–37 (B)	Week 38–42 (C)		
HSD17Bs + AKR1Cs, reduction↘, oxidation↗							
	UA	Allopregnanolone/5α-dihydroprogesterone*** a	0.2 (0.169, 0.225)	0.21 (0.189, 0.233)	0.119 (0.1, 0.145)	A > C***, B > C***	↗
	UV≈	Allopregnanolone/5α-dihydroprogesterone***	0.188 (0.148, 0.232)	0.192 (0.168, 0.265)	0.113 (0.091, 0.139)	A > C***, B > C***	↗
	UA	Pregnanolone/5β-dihydroprogesterone	1.32 (1.14, 1.63)	1.45 (1.21, 1.74)	1.18 (0.902, 1.44)		~
	UV***↓	Pregnanolone/5β-dihydroprogesterone*	0.601 (0.484, 0.878)***	0.836 (0.67, 1.11)**	0.577 (0.447, 0.794)***	B > C*	↗
	UA	Allopregnanolone/isopregnanolone*	0.553 (0.468, 0.635)	0.536 (0.502, 0.592)	0.503 (0.418, 0.566)		↗
	UV***↑	Allopregnanolone/isopregnanolone**	0.8 (0.683, 0.983)**	0.991 (0.602, 1.13)***	0.574 (0.464, 0.918)***	A > C*, B > C*	↗
	UA	Pregnanolone/epipregnanolone	8.32 (7.81, 9.51)	8.34 (7.27, 9.73)	10 (8.11, 12.3)		~
3α-OH/3-oxo /3β-OH	UV***↓	Pregnanolone/epipregnanolone	6.66 (5.89, 7.86)**	6.78 (5.67, 8.17)	6.77 (5.41, 8.24)***		~
	UA	5α-Pregnane-3α,20α-diol/5α,20α-tetrahydroprogesterone	0.0373 (0.0276, 0.0876)	0.0419 (0.0304, 0.0516)	0.0523 (0.0352, 0.072)		~
	UV*↓	5α-Pregnane-3α,20α-diol/5α,20α-tetrahydroprogesterone	0.0363 (0.0229, 0.0882)	0.0315 (0.0262, 0.0467)	0.0401 (0.027, 0.0526)*		~
	UA	5β-Pregnane-3α,20α-diol/5β,20α-tetrahydroprogesterone	0.983 (0.739, 1.13)	0.733 (0.616, 0.91)	0.789 (0.602, 0.981)		~
	UV***↓	5β-Pregnane-3α,20α-diol/5β,20α-tetrahydroprogesterone	0.304 (0.25, 0.516)***	0.284 (0.234, 0.498)**	0.278 (0.206, 0.363)***		~
	UA	5α-Pregnane-3α,20α-diol/5α-pregnane-3β,20α-diol	1.12 (0.885, 2.32)	1.1 (1.03, 1.25)	1.31 (0.99, 1.83)		~
	UV***↓	5α-Pregnane-3α,20α-diol/5α-pregnane-3β,20α-diol	1.02 (0.586, 2.02)	1.08 (0.506, 1.26)	0.823 (0.467, 1.19)***		~
	UA	5β-Pregnane-3α,20α-diol/5β-pregnane-3β,20α-diol**	40.6 (28.8, 70.8)	25.9 (19.8, 27.8)	28.1 (24, 37.7)	A > B**	↗
	UV***↓	5β-Pregnane-3α,20α-diol/5β-pregnane-3β,20α-diol	20.4 (15, 70.8)	15.1 (11.3, 24.3)**	14.6 (11.4, 19.1)***		~
	UA	Androstenediol/DHEA***	0.0656 (0.0525, 0.0913)	0.0334 (0.0236, 0.0909)	0.0271 (0.021, 0.0391)	A > B*, A > C***	↗
	UV***↑	Androstenediol/DHEA***	0.121 (0.0819, 0.193)**	0.0724 (0.0347, 0.132)	0.0335 (0.0261, 0.0473)**	A > C***, B > C**	↗
	UA	Testosterone/androstenedione***	2.36 (1.36, 3.05)	1.01 (0.542, 1.52)	0.35 (0.208, 0.478)	A > C***, B > C**	↗
17β-OH/17-oxo	UV≈	Testosterone/androstenedione***	1.69 (0.959, 2.86)	0.938 (0.491, 1.39)	0.578 (0.413, 0.834)**	A > C***	↗
	UA	Estradiol/estrone***	0.434 (0.381, 0.561)	0.258 (0.171, 0.499)	0.214 (0.186, 0.275)	A > C***	↗
	UV***↓	Estradiol/estrone*	0.183 (0.153, 0.365)***	0.175 (0.117, 0.511)	0.137 (0.103, 0.194)***	A > C*	↗
	UA	20α-Dihydropregnenolone/pregnenolone*	0.078 (0.066, 0.136)	0.127 (0.093, 0.138)	0.081 (0.064, 0.123)	B > C*	↗
	UV***↓	20α-Dihydropregnenolone/pregnenolone**	0.0597 (0.0514, 0.0823)*	0.0764 (0.0576, 0.122)*	0.0506 (0.0402, 0.0713)***	B > C**	↗
	UA	20α-Dihydroprogesterone/progesterone**	0.151 (0.010, 0.192)	0.19 (0.138, 0.308)	0.112 (0.072, 0.153)	B > C**	↗
	UV***↓	20α-Dihydroprogesterone/progesterone*	0.037 (0.028, 0.092)***	0.075 (0.051, 0.121)**	0.032 (0.026, 0.054)***	B > C*	↗
	UA	5α,20α-Tetrahydroprogesterone/5α-dihydroprogesterone***	2.42 (1.94, 2.77)	2.78 (2.31, 3.7)	1.48 (1.21, 1.87)	A > C***, B > C***	↗
	UV***↓	5α,20α-Tetrahydroprogesterone/5α-dihydroprogesterone***	1.61 (1.18, 2.32)**	2.02 (1.68, 2.44)**	1.24 (1.05, 1.45)***	A > C*, B > C***	↗
	UA	5α-Pregnane-3α,20α-diol/allopregnanolone	0.47 (0.409, 0.955)	0.567 (0.419, 0.697)	0.557 (0.499, 0.837)		~
	UV***↓	5α-Pregnane-3α,20α-diol/allopregnanolone	0.367 (0.22, 0.755)*	0.359 (0.269, 0.426)***	0.406 (0.358, 0.568)***		~
20α-OH/20-oxo	UA	5α-Pregnane-3β,20α-diol/isopregnanolone	0.223 (0.196, 0.288)	0.265 (0.224, 0.355)	0.241 (0.196, 0.298)		~
	UV***↑	5α-Pregnane-3β,20α-diol/isopregnanolone	0.295 (0.244, 0.452)**	0.348 (0.244, 0.526)**	0.316 (0.252, 0.426)***		~
	UA	5β,20α-Tetrahydroprogesterone/5β-dihydroprogesterone**	2.12 (1.63, 2.79)	2.81 (2.17, 4.24)	1.73 (1.29, 2.15)	B > C*	↗
	UV≈	5β,20α-Tetrahydroprogesterone/5β-dihydroprogesterone***	1.95 (1.33, 2.66)	2.72 (2.17, 3.47)	1.69 (1.28, 2.08)	A < B*, B > C***	⊂
	UA	5β-Pregnane-3α,20α-diol/pregnanolone*	1.54 (1.21, 2.15)	1.47 (1, 1.86)	1.17 (0.935, 1.42)		↗
	UV***↓	5β-Pregnane-3α,20α-diol/pregnanolone**	1.12 (0.721, 1.5)***	0.968 (0.858, 1.42)**	0.773 (0.625, 1.02)***	A > C*, B > C*	↗
	UA	5β-Pregnane-3β,20α-diol/epipregnanolone**	0.292 (0.198, 0.425)	0.509 (0.36, 0.626)	0.396 (0.313, 0.44)	A < B**	↗
	UV≈	5β-Pregnane-3β,20α-diol/epipregnanolone	0.292 (0.173, 0.424)	0.441 (0.27, 0.626)	0.376 (0.239, 0.474)		~

Table 4
Relationships between GA at preterm and term deliveries and ratios of steroid polar conjugates to unconjugated steroids in umbilical blood (expressed as median (quartiles)), unpublished data. For details see Table 1.

Conjugated/unconjugated steroid		GA at labor			Differences[b], dependence on GA	
		Week 28–32 (A)	Week 33–37 (B)	Week 38–42 (C)		
Pregnenolone^{***,a}	UA	30.9 (15.8, 43.2)	108 (56.5, 168)	95.1 (69, 129)	A < B***, A < C***	↗
Pregnenolone***	UV^{*,c}↓	33.9 (23, 54.1)^{*,c}	91.2 (36, 132)*	70.3 (54.2, 112)*	A < B**, A < C***	↗
17-Hydroxypregnenolone***	UA	3.94 (2.1, 9.89)	35.4 (21.6, 75.2)	17.9 (7.99, 31.9)	A < B***, A < C**, B > C***	∩
17-Hydroxypregnenolone***	UV***↑	8.59 (5.45, 16.4)**	77.4 (35.7, 168)**	49.9 (31.6, 138)***	A < B***, A < C***	↗
20α-Dihydropregnenolone***	UA	255 (178, 442)	498 (394, 775)	606 (478, 915)	A < C***	↗
20α-Dihydropregnenolone***	UV***↑	336 (206, 516)	693 (516, 922)*	926 (715, 1190)***	A < C***	↗
16α-Hydroxypregnenolone***	UA	0.252 (0.149, 0.328)	0.922 (0.371, 1.52)	0.798 (0.465, 1.41)	A < B**, A < C***	↗
16α-Hydroxypregnenolone*	UV***↑	1.24 (0.968, 2.43)**	2.73 (1.22, 4.24)***	2.43 (1.73, 4.43)***	A < C*	↗
Dehydroepiandrosterone***	UA	62.5 (36.4, 84.3)	205 (176, 355)	153 (109, 224)	A < B***, A < C***	↗
Dehydroepiandrosterone*	UV***↑	341 (213, 533)***	739 (406, 964)***	556 (279, 809)***	A < B*	↗
16α-Hydroxy-DHEA	UA	146 (38, 725)	194 (92.4, 417)	137 (45.5, 221)		~
16α-Hydroxy-DHEA	UV**↓	149 (93.6, 372)	127 (81.1, 217)*	91 (33.5, 170)		~
Androstenediol***	UA	426 (310, 675)	5040 (1520, 10,000)	10,600 (5880, 13,600)	A < B***, A < C***	↗
Androstenediol***	UV***↑	1750 (601, 2560)***	10,400 (2090, 19,400)**	32,700 (15,900, 46,000)***	A < B**, A < C***, B < C**	↗
5-Androstene-3β,7α,17β-triol***	UA	3.93 (1.42, 7.58)	16.6 (10.6, 35.1)	23.1 (11.2, 37.6)	A < B***, A < C***	↗
5-Androstene-3β,7α,17β-triol***	UV***↑	11.6 (5.79, 33.5)***	53.7 (23.1, 152)**	56 (35.4, 100)***	A < B*, A < C***	↗
5-Androstene-3β,7β,17β-triol***	UA	2.91 (1.6, 4.63)	19.7 (8.3, 33.7)	37.7 (24.3, 58.4)	A < B**, A < C***	↗
5-Androstene-3β,7β,17β-triol***	UV***↑	6.62 (4.26, 17.8)***	20.5 (7.63, 38.3)	59.3 (35.9, 116)**	A < C***, B < C**	↗
17-Hydroxyprogesterone	UA	0.34 (0.325, 0.706)	0.764 (0.688, 1.12)	0.868 (0.684, 1.04)		~
17-Hydroxyprogesterone	UV***↓	0.464 (0.317, 0.636)	0.48 (0.447, 0.637)*	0.749 (0.455, 0.902)**		~
20α-Dihydroprogesterone***	UA	0.494 (0.392, 0.713)	0.883 (0.669, 1.09)	1.12 (0.725, 1.75)	A < C***	↗
20α-Dihydroprogesterone*	UV***↑	0.943 (0.576, 1.65)***	1.73 (0.937, 2.26)***	1.95 (1.26, 2.9)***	A < C*	↗
Androsterone**	UA	33 (14.4, 61.9)	83 (60.5, 188)	81.2 (53.7, 166)	A < B*, A < C**	↗
Androsterone**	UV***↑	78 (39, 165)***	172 (141, 361)***	231 (122, 321)***	A < B*, A < C**	↗
Etiocholanolone*	UA	22.2 (8.98, 57.3)	68.8 (41.5, 112)	45.3 (29.4, 93.8)	A < B*, A < C*	↗
Etiocholanolone	UV≈	35.6 (13.7, 72.4)	57.3 (33.8, 109)	49.8 (24.2, 81.1)		~
Estrone***	UA	17 (8.15, 24.7)	31.7 (12.1, 46.3)	8.01 (5.17, 14.3)	B > C***	↘
Estrone***	UV***↓	2.18 (1.18, 3.13)***	5.64 (2.16, 9.06)***	1.56 (0.99, 2.28)***	B > C***	↘
Estradiol***	UA	10.8 (9.39, 15.5)	12.5 (9.83, 25.9)	3.53 (2.37, 5.31)	A > C***, B > C***	↘
Estradiol***	UV***↓	2.77 (1.96, 3.13)***	3.19 (2.55, 4.18)***	1.2 (0.993, 1.54)***	A > C***, B > C***	↘
Estriol***	UA	89.9 (49.4, 120)	178 (89.8, 330)	65.7 (35.6, 98.1)	A < B*, B > C***	∩
Estriol***	UV***↓	8.43 (6.24, 14.2)***	32.8 (23.3, 47.1)***	12.1 (8.47, 17.6)***	A < B***, B > C***	∩
Allopregnanolone***	UA	16.5 (13, 27.1)	102 (68.3, 155)	41.8 (34.2, 63.5)	A < B***, A < C***, B > C**	∩
Allopregnanolone***	UV***↑	26 (19.7, 38.2)**	104 (63.3, 224)	65.3 (44, 81.9)***	A < B***, A < C***	↗
Isopregnanolone***	UA	7.82 (5.13, 12)	28.8 (19.9, 54.5)	30.7 (22.6, 42)	A < B***, A < C***	↗
Isopregnanolone***	UV***↑	15 (9.73, 22.8)***	44.4 (28.4, 63.1)**	46.8 (29.7, 67.2)***	A < B***, A < C***	↗
Pregnanolone***	UA	4.75 (3.42, 8.52)	22.3 (13.9, 40.6)	16.8 (12.1, 24.7)	A < B***, A < C***	↗
Pregnanolone***	UV***↑	14.6 (8.77, 21.3)***	42.4 (30.3, 94.4)***	41.4 (33.6, 56.5)***	A < B***, A < C***	↗
Epipregnanolone***	UA	12 (10.4, 18.9)	64.9 (31.8, 126)	46.9 (36.1, 66.3)	A < B***, A < C***	↗
Epipregnanolone***	UV***↑	29.9 (20.5, 52)***	128 (44, 244)***	87.2 (66.4, 136)***	A < B***, A < C**	↗
5α,20α-Tetrahydroprogesterone***	UA	1.08 (0.666, 1.72)	3.02 (2.17, 4.23)	1.77 (1.19, 2.35)	A < B***, A < C*, B > C*	∩
5α,20α-Tetrahydroprogesterone**	UV***↑	1.66 (1.17, 2.5)***	3.74 (2.24, 5.92)*	2.23 (1.71, 3.59)*	A < B**	↗
5α-Pregnane-3α,20α-diol***	UA	229 (102, 408)	1100 (623, 1480)	247 (185, 354)	A < B***, B > C***	∩
5α-Pregnane-3α,20α-diol***	UV***↑	439 (215, 660)***	1460 (1020, 1930)**	470 (364, 962)***	A < B***, B > C**	∩
5α-Pregnane-3β,20α-diol***	UA	316 (185, 437)	1280 (891, 1610)	636 (453, 975)	A < B***, A < C**, B > C*	∩
5α-Pregnane-3β,20α-diol***	UV***↑	476 (251, 819)**	1340 (879, 1920)	773 (519, 1030)*	A < B***, B > C*	∩
5β,20α-Tetrahydroprogesterone*	UA	1.26 (0.835, 3.67)	3.34 (2.31, 3.69)	3.03 (2.15, 4.78)	A < C*	↗
5β,20α-Tetrahydroprogesterone*	UV***↑	2.15 (1.24, 5.68)*	3.63 (2.34, 5.17)	4.3 (2.58, 7.57)*	A < C*	↗
5β-Pregnane-3α,20α-diol***	UA	40.7 (28.8, 55.5)	160 (133, 227)	113 (85.6, 194)	A < B***, A < C***	↗
5β-Pregnane-3α,20α-diol***	UV***↑	153 (97.1, 224)***	521 (363, 629)***	363 (225, 483)***	A < B***, A < C**	↗
5β-Pregnane-3β,20α-diol*	UA	285 (169, 766)	816 (541, 1270)	723 (508, 1030)	A < B*, A < C*	↗
5β-Pregnane-3β,20α-diol	UV***↑	501 (312, 2130)*	1510 (968, 3040)***	1300 (825, 2040)***		~

↗: increasing trend with GA; ~: no change with GA; ↘: decreasing trend with GA; ∩: maximum in Group B; ↑: higher values in UV; ↓: lower values UV; ≈: no significant difference between UA and UV.

[a] Kruskal–Wallis test.
[b] Dunn's multiple comparisons with Bonferroni correction.
[c] Wilcoxon's paired test.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

(FZ) of fetal adrenal (FA) in the fetal steroidogenesis. Significant steroidogenic activity of this tissue producing substantial amounts of conjugated (mainly sulfated) Δ^5 steroids is under the control of placental corticotropin (CRH) [32]. The overproduction of sulfated Δ^5 steroids provides precursors for placental synthesis of estrogens and progestogens. Additionally, the huge amounts progestogens and their metabolites protect the fetal central nervous system (CNS) from oxidation stress and neuroexcitatory estrogens.

2.1.2. Umbilical arteriovenous differences and fetomaternal differences

Despite the huge placental expression of steroid sulfatase (STS) [33] hydrolyzing the sulfated Δ^5 steroids from the fetus (see Review [13]), their placental extraction is limited and the majority of these substances reappear unconverted in the fetal circulation as documented by their only slightly positive umbilical arteriovenous differences (AVD) [34] (Table 1).

Like the sulfated Δ^5 steroids, some of their unconjugated counterparts like DHEA and Preg17 [2,24,35–39] (Table 1) show slightly higher levels in UA than in UV (positive AVD). Alternatively, the unconjugated pregnenolone shows negative (−32%) or insignificant AVD [34,36,37] (Table 1). When compared with UA, UV, MV, the highest levels of unconjugated pregnenolone at delivery are present in the blood from retroplacental space (RPS)[39]. This data also demonstrate that placenta is a key organ producing unconjugated pregnenolone at least in the fetus.

In the case of 16α-hydroxylated Δ^5 steroids, the results vary more. Chang et al. [34] report negative AVD for unconjugated 16α-hydroxy-DHEA (−43%) while Laatikainen et al. [37] document positive AVD for sulfated 16α-hydroxy-DHEA and we surprisingly recorded the negative ones in both cases (Table 1). There is a question whether the positive AVD for DHEA but the markedly negative ones for pregnenolone and 16α-hydroxy-DHEA may be ascribed to specific placental metabolism for the 16α-hydroxy-steroids.

Due to excessive steroidogenic activity and concomitantly significant activity of the cytosolic, 2A, dehydroepiandrosterone-preferring, member 1 sulfotransferase (SULT2A1) in the FZ, the conjugated Δ^5 steroids and unconjugated pregnenolone as well as total amounts of the C21 Δ^5 steroids in the fetal circulation at labor show consistently higher levels when compared with those in the maternal venous blood (MV) [13,15,24,40–42] (Table 1). On the other hand, there is probably no significant difference between Preg17 levels in MV and UV [40]. DHEA levels are comparable in UA and MV but notably lower in UV. The unconjugated androstenediol shows slightly but significantly higher levels in UA when compared with MV [24]. DHEA and androstenediol are promptly converted to androstenedione and testosterone, respectively, by specific, placental type 1 3β-hydroxysteroid dehydrogenase (HSD3B1) and the created C19 Δ^4 steroids are further transformed to estrogens by placental aromatase (CYP19A1). Concerning the origin of Preg17 and Preg17S, Belisle et al. [40] suggested that maternal adrenals provide both steroid forms in the maternal circulation, while the FZ primarily synthesizes these steroids in the fetus. On the other hand, our data demonstrate the same shape of the profile in mother and fetus and marked positive arteriovenous (Table 1) and fetomaternal differences for these steroids [13,23], which points to their mostly fetal origin.

Based on the AVD, Mathur et al. [36] assessed that placenta clears about 25% and 30% of DHEAS and PregS, respectively [36], and Laatikainen et al. [37] estimated daily amounts of fetal Δ^5 steroids metabolized by the placenta for pregnenolone (0.6 mg), PregS (21 mg), DHEA (0.5 mg), DHEAS (34 mg), and 16α-hydroxy-DHEA (134 mg).

2.1.3. Correlations of Δ^5 steroids between fetal and maternal body fluids in pregnancy

Sulfated Δ^5 steroids strongly correlate between UA and UV but a different situation is evident in the case of their unconjugated counterparts [34,36]), which is compatible with the limited placental extraction for the sulfated Δ^5 steroids when compared to their unconjugated counterparts. Our current unpublished data confirms the strong correlations between the steroid sulfates but show strong or at least medium correlations even for the unconjugated Δ^5 steroids (Table 2, Figs. 2 and 3) even if the corresponding correlation coefficients are slightly lower in the later substances. Relatively weak and medium correlations between mixed umbilical arterial and venous blood (UM) an MV for DHEA and DHEAS were reported in the literature [43]. Based on this data Troisi et al. [43] pointed to possible misclassification when using maternal data to predict steroid levels in the fetus.

2.1.4. Changes of Δ^5 steroids in fetal blood during pregnancy and around parturition

Although corticotropin (CRH) is a key regulator of steroidogenic activity in the FZ, its efficiency in predicting fetal maturity is low [32]. Therefore, we recently completed multivariate regression models based on multicomponent steroids analysis in individual fetal and maternal body fluids (UA, UV, MV and AF) at premature and in term deliveries (week 28–41 of gestation) based on the GC–MS platform and the steroid metabolome substantially better predicted the fetal maturity when compared with the predictivity of CRH. This was most probably due to the high stability of the steroids and multicollinearity between the steroid predictors amplifying predictivity of the models. From the steroids enrolled in the model, the Δ^5 steroids exhibited high predictivity for UA and UV but less efficiency for MV and AF. This was probably due to the greater distance of MV and AF from the primary source of the sulfated Δ^5 steroids in the FZ. Several catabolites of C19 Δ^5 steroids, like their 16α-hydroxymetabolites, conjugated epiandrosterone and conjugated 5-androstene-3β,7α/β,17β-triols, were excellent predictors, possibly due to their higher stability in body fluids than in the case of the parent substances [2], which conforms with a report from Laatikainen et al. [37] who suggested that DHEAS and PregS in the cord blood better reflects the function of the FZ than their unconjugated counterparts.

In the case of conjugated androstenediol showing the most pronounced and escalating increase in the 3rd trimester in maternal and fetal body fluids, our findings [2,24] are compatible with those from others [29,39]. Huhtaniemi and Vihko [29,39] show a pronounced increase of the steroid conjugate at week 10–20 of pregnancy in UM and Riepe et al. [39] demonstrate strongly positive correlation of conjugated androstenediol with GA at delivery. In contrast to our recently published [2,13] and current unpublished data (Table 1) showing increasing levels in all conjugated Δ^5 steroids at least between week 28–37 of gestation, Huhtaniemi and Vihko [29] report relative independence of other conjugated Δ^5 steroids (polar conjugates of pregnenolone, DHEA, 16α-hydroxy-DHEA, 3β,17β-dihydroxy-5-androsten-16-one, 20α-dihydropregnenolone) on GA and others demonstrate even decreasing DHEAS concentrations in umbilical circulation from midgestation to term [44,45]. From the unconjugated Δ^5 steroids at delivery, only androstenediol shows significant negative correlations with GA in UA, UV and AF but a significantly positive one in MV, while the remaining ones correlate either positively with GA or do not correlate [2,39] (Table 1).

Although the Preg17 to pregnenolone ratio in MV is nearly constant during labor and the 1st day postpartum, that of DHEA to Preg17 rises, which indicates increased C17,20 side chain cleavage activity and suppressed C17-hydroxylation activity even if both metabolic steps are catalyzed by the same enzyme CYP17A1 [23]. This is in line with the data of Soucy and Luu-The [46] demonstrating that higher substrate to enzyme ratio prefers the higher C17-hydroxylation activity over C17,20-side chain cleavage activity. After 12 h postpartum, the early preterm neonates show about 2–3 times higher levels of pregnenolone and Preg17 as compared to the full-term newborns [39]. Riepe et al. [39] ascribes this finding to a greater stress response of the premature neonate. However, there may be another explanation that is linked to the relative immaturity of FA in the preterm infants resulting in slower postpartum adaptation of neonatal adrenals when compared with those of the full-term newborns.

Despite some controversies, the aforementioned data point to increasing production of conjugated Δ^5 steroids (serving as precursors for the placental synthesis of female sex hormones) with advancing GA.

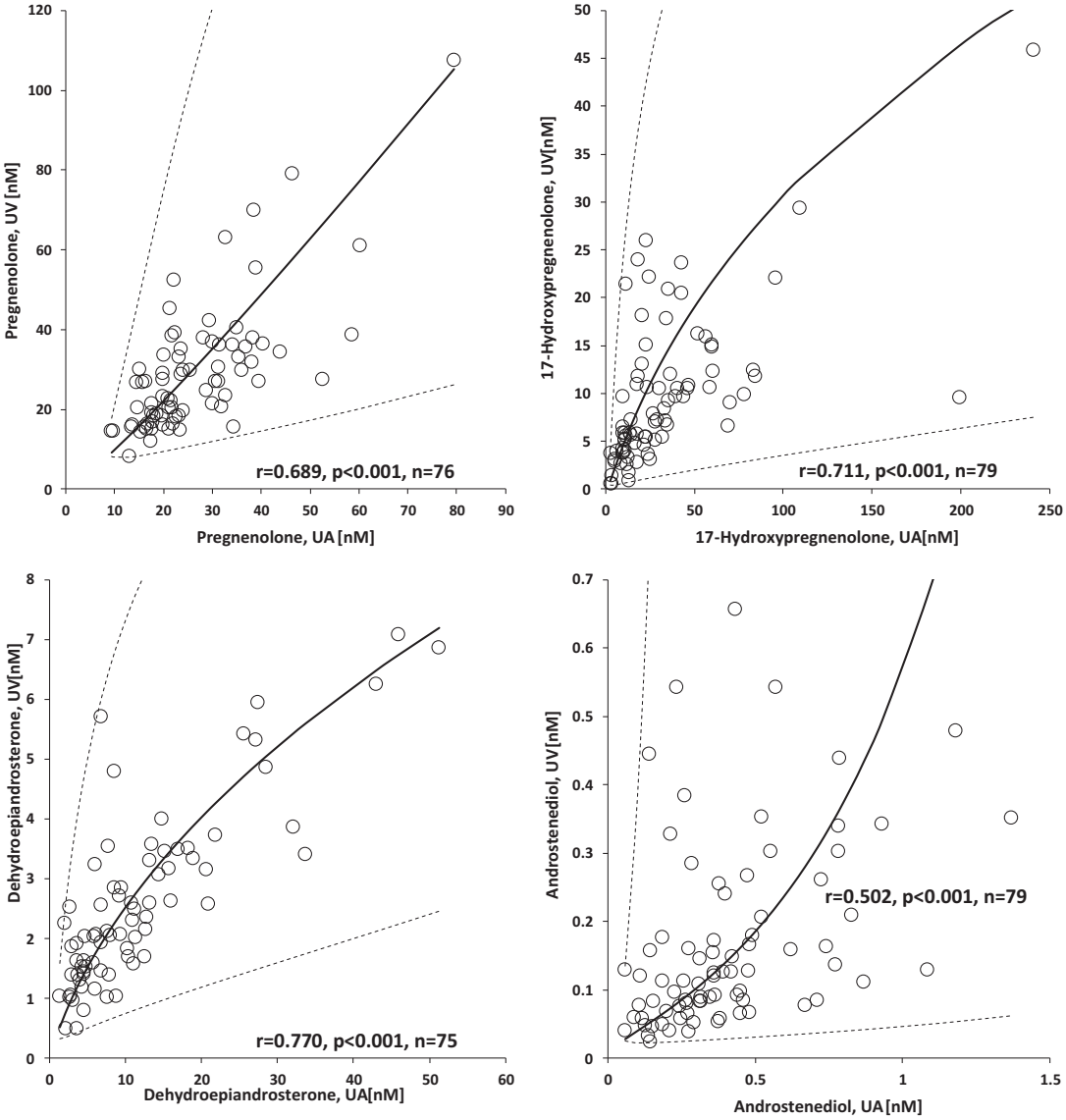

Fig. 2. Correlations of unconjugated Δ^5 steroids between umbilical arterial and venous blood at labor. The full and dashed curves represent the retransformed principal axis and retransformed 95% confidence interval calculated from the data transformed by power transformations for attaining Gaussian data distribution and constant variance. The symbols *r*, *p*, and *n* represent correlation coefficient, its statistical significance and number of measurements, respectively, for correlations between the transformed variables. UA: umbilical artery, UV: umbilical vein.

2.2. Progestogens

2.2.1. Levels of progestogens in fetal body fluids and tissues

Like the levels of sulfated Δ^5 steroids, progestogen concentrations are exceedingly elevated in fetal circulation when compared to the situation in non-pregnant women [13,19,20,24] (Table 1). Whereas progesterone levels in the follicular phase of non-pregnant women are below 6 nM, fetal progesterone in UV reaches micromolar concentrations [24] (Table 1).

Progestogens are also abundant in various fetal tissues. For instance, progestogen levels in fetal tissues displayed as mean (maximum) are as follows (pmol/g): Progesterone: brain 660 (2471), placenta 6069 (15,509), skin 698 (1509), lung 912 (3287), liver 610 (3018), kidney 1609 (5341), intestine 1310 (3345), myometrium 254 (1536); 20α-dihydroprogesterone (Prog20α): myometrium 47 (178) [18,47]. Progesterone concentrations in adrenals at week 11–24 of gestation expressed as mean (SD) are 942 (287) pmol/g and Prog20α levels in fetal tissues are like this: brain 277 (142), placenta 1468 (496), adrenals 811 (620), lung 192 (84), liver 303 (286), kidney 244 (137), intestine 248 (163) [48].

2.2.2. Umbilical arteriovenous differences and fetomaternal differences

Higher progestogen levels are present in UV when compared with UA [18,24,37,49–53] (Table 1), which demonstrates their placental origin. The fetus clears about 50% and 25% of progesterone and 17-hydroxyprogesterone (Prog17), respectively, [36] and the daily amount of fetal progesterone metabolized by the placenta at term is about 14 mg [37]. When compared to MV, the progestogen levels are higher in UV and UA [18,24,49–53].

2.2.3. Correlations of progestogens between fetal and maternal body fluids in pregnancy

Various authors show moderate or even strong correlations between UA and UV for progesterone [49,51]. Our current unpublished data show strong correlations between UA and UV for all progestogens except progesterone that shows medium arteriovenous correlation (Table 2).

Within the fetal circulation, progesterone significantly correlates with estrogens [54] but fetomaternal correlation, correlation

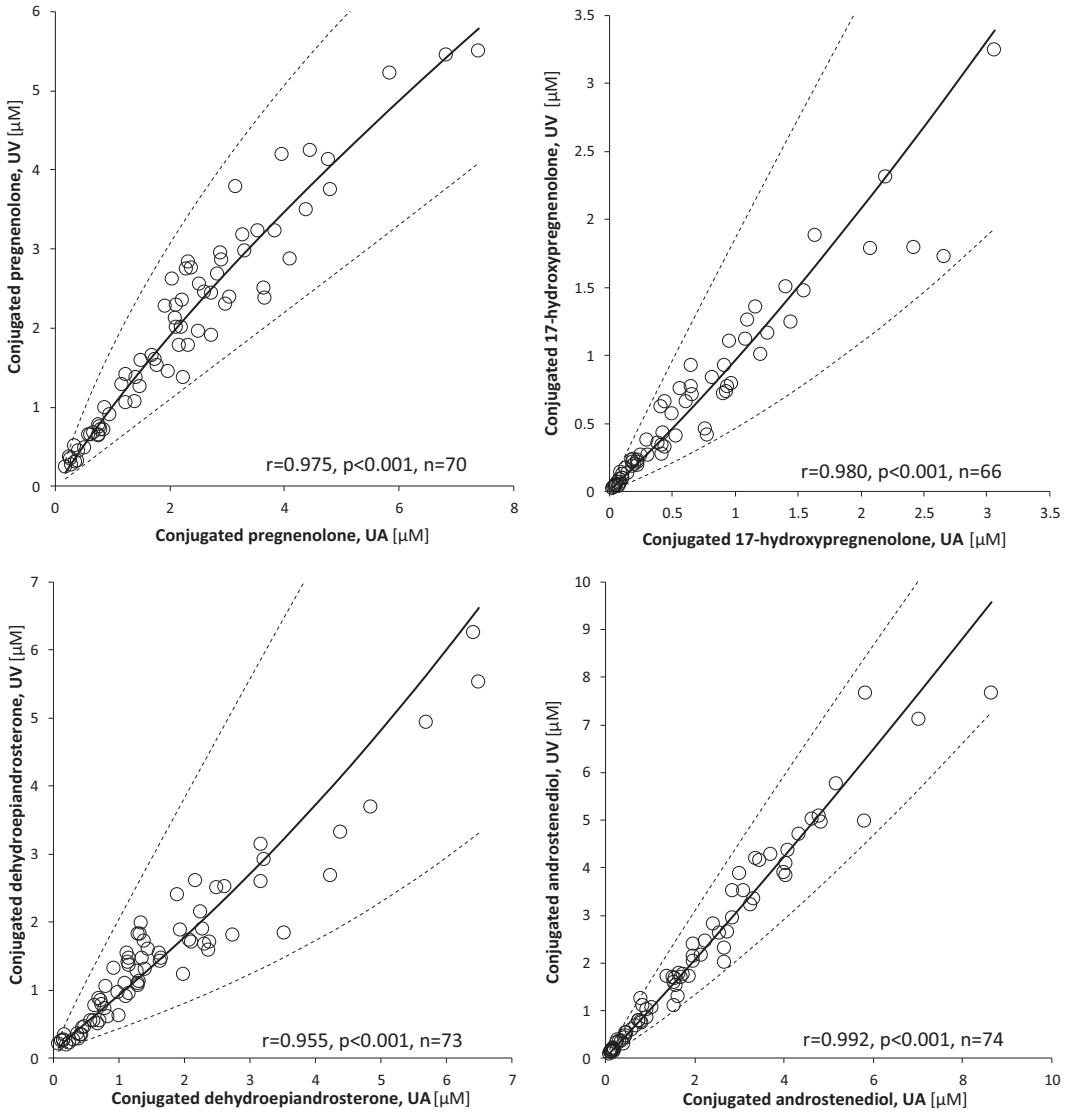

Fig. 3. Correlations of conjugated Δ^5 steroids between umbilical arterial and venous blood at labor. The drawings and symbols are the same as for Fig. 2.

between blood from umbilical cord and RPS [49,51,54] and correlations between fetal progesterone and steroids in the MV [54] are absent.

2.2.4. Changes of progestogens in fetal blood during pregnancy and around parturition

Prog17 levels in UA and UV escalate from week 33 of gestation [50] (Table 1). Tulchinsky and Simmer [50] suggested primarily placental production of Prog17 from the precursors originating in the FA (PregS) and assessed 10–20 times higher placental production of Prog17 at term compared to the situation in midpregnancy and 90% contribution of placental Prog17 in the maternal Prog17.

Contradictory data were published concerning the progesterone in the fetal circulation. Hercz et al. [51] display an increasing trend in UA and UV progesterone during week 28–36 of gestation followed by a plateau and then by a drop from week 40. Donaldson et al. [45] indicate that progesterone in UA of unstressed fetuses do not exhibit a significant trend (week 18–41 of gestation) while our recent data shows a moderate but significant progesterone increase in UA and UV at labor between the week 36–41 of gestation [13]. Progesterone levels in MV, decidua, myometrium and placenta [58,59] are unchanged from midpregnancy to term but escalate in decidua at term, while the ratios of pregnancy-sustaining progesterone to parturition-inducing estradiol generally decrease from midpregnancy to term.

In MV, progesterone linearly increases from 98 nM in the week 18–783 nM in the week 41 of gestation [45]. The fall in progesterone and total Prog20α from the pre-labor pain to delivery in MV points to the reduction of placental HSD3B1 activity, which might be reflected by raised uterine activity at labor [15].

2.2.5. Placental and fetal interconversion of progesterone and 20α-dihydroprogesterone

20α-Dihydroprogesterone (Prog20α) levels in UA, UV, RPS, and MV are considerably lower than those of progesterone [18,49,50] (Table 1). Runnebaum et al. [18] show about twice as high mean progesterone levels in UV (2.24 μM) than in the UA (1.03 μM) but no AVD for the Prog20α (54 nM for both UV and UA) and the authors did not suppose there was an importance for the Prog20α in the placental progesterone production near term. Nevertheless, Runnebaum's findings and our own recently published [2,13,24,31] and current unpublished data (Tables 1 and 3) are compatible with the concept suggesting that the progesterone secreted by placenta is readily converted into Prog20α in the fetus by reductive isoforms of 17β-hydroxysteroid dehydrogenases (HSD17Bs) and perhaps also by some isoforms from family 1C aldoketoreductases (AKR1Cs)

[2,13,24,31]. The mean Prog20α to mean progesterone ratios in the Runnebaum's data are 2 and 2.2 times higher in UA compared to UV and our current unpublished results show analogous values from 2.5 to 4.1 and significant AVD in all groups assorted according to the GA (Table 1). The Prog20α to progesterone ratio in the Runnebaum's data is 5.5 times higher in MV compared to UV and our data shows a close value 4.8 [24], which is compatible with our concept suggesting dominance of progestogens, estrogens and GABAergic steroids in oxidized and reduced forms at the placental output into the fetal and maternal compartment, respectively.

2.2.6. Origin of progesterone in pregnancy

Tulchinsky and Simmer [50] suggested primarily placental production of Prog17 from the precursors originating in the FZ (PregS and Preg17S) and assessed about 90% contribution of placental Prog17 in the total circulating maternal Prog17. In contrast to the levels of Δ^5 steroids and estrogens being markedly lower in anencephalic fetuses, the progesterone levels in this case do not differ significantly from those in normal fetuses [15]. Based on this data and the absence of correlation between maternal and fetal progesterone, some authors suggest independent progesterone placental secretion to the mother and to the fetus but found no physiological role for the fetal progesterone [49,51] (see Review [13]). However, others (including us), suggest that PregS originating in the FZ is a key progesterone precursor. Only in situations in which the fetal production of PregS decreases does the placenta primarily synthesize the pregnenolone and progesterone from the maternal cholesterol [2,15,24,31,50,55–57].

2.3. Estrogens

2.3.1. Levels of estrogens in fetal circulation, comparison with the situation in non-pregnant women

As in the case of Δ^5 steroids and progestogens, the concentrations of unconjugated and conjugated estrone in umbilical blood are excessive [13,20,21,24,60] (Table 1). In contrast to non-pregnant women having negligible estriol concentrations [61], estriol dominates in the fetal circulation over the remaining estrogens, representing about 78% of unconjugated and 95% of the conjugated estrogens irrespectively of the GA [62]. Serum 16α-hydroxyestrone levels in the samples obtained from anencephalic pregnancy are significantly lower than those in normal pregnancy, demonstrating that the fetal adrenal function is involved in the formation of estrogens during pregnancy [41].

2.3.2. Umbilical arteriovenous differences and fetomaternal differences

Various authors (including us) demonstrate several times higher concentrations of unconjugated estrone estradiol, 16α-hydroxy-estrone and estriol in UV when compared with UA [2,24,31,36,37,41,54,62,63] (Table 1). In estrogen polar conjugates (mostly sulfates in the fetus [64]) some authors do not report significant AVD [62] but others [37] (including us [24] (Table 1)) indicate slightly but significantly positive AVD for conjugates of estrone and estriol. The aforementioned data demonstrates that estrogens are secreted from the placenta into the fetus in the unconjugated form [62] due to extensive expression and activity of steroid sulfatase (STS) in human placenta (for review [13]). On the other hand, slightly positive AVD for sulfates of estrone and estriol as well as high expression of estrogen-preferring sulfotransferase (SULT1E1) in FZ and fetal liver point to intensive sulfation of estrone and estriol in the fetal compartment, which may be a part of the protective mechanism against fetal hyperestrogenization (concomitantly with 16α-hydroxylation of estrogens and estrogen precursors in the fetal liver catalyzed by cytochrome P450 CYP3A7 enzyme (CYP3A7) and estradiol oxidation to estrone catalyzed by oxidative isoforms of HSD17B in the placental zones that are in close contact with the fetal circulation).

There are significantly lower levels of unconjugated and conjugated estradiol in UV when compared with MV [13,24,63,65,66] while the difference for unconjugated estrone is either not significant [24,63] or slightly higher in UV [13,65]. Estradiol clearly prevails over estrone in MV but the opposite is found in the UV [13,24,54,63,65] (Table 1). Patten et al. [65] discussed large amounts of estradiol, which are effectively oxidized to estrone during the transplacental passage. The aforementioned data as the concept of Patten et al. [65] are compatible with our concept suggesting dominance of oxidized and reduced forms of bioactive steroids at the placental output into the fetal and maternal compartment, respectively [2,13,24,31].

The levels of conjugated estrone are pronouncedly higher in MV when compared to UV [13,24], probably due to extensive conjugation of estrone not only in the fetus but also in the maternal compartment. On the other hand, the concentrations of 16α-hydroxy-estrogens (free and conjugated estriol and 16α-hydroxy-estrone) are pronouncedly higher in UV when compared with MV [24,41,66] which attests to their fetal origin. Estriol glucuronide is a major conjugate of estriol in maternal plasma [62] but only a minor conjugate of estriol in fetal plasma where the polar conjugates are dominantly represented by estriol sulfate [64].

The fetus clears about 48% of estradiol [36] and the daily amount of fetal estriol sulfate metabolized by the placenta and daily provision of the fetus by placental estradiol is 36 mg and 0.8 mg, respectively [37].

2.3.3. Correlations of estrogens between fetal and maternal body fluids in pregnancy

Data in the literature demonstrate moderate or strong correlations between estrogens within UA and UV [54], and our current unpublished data show strong arteriovenous correlations for both unconjugated and conjugated estrogens (Table 2). As in the case of progestogens, the estrogen correlations between fetal and maternal estrogens are weak or absent with only the estriol strongly correlating between UA and MV and moderately between UV and MV [43,54].

2.3.4. Changes of estrogens in fetal and maternal compartments

Both unconjugated and sulfo-conjugated total estrogens (estrone + estradiol + estriol) in human fetal plasma rise 5–6 times during week 17–35 of gestation [62]. Similarly, the estrone and 16α-hydroxyestrone show about a 7-fold rise in UA, UV, placenta, and MV between the 1st and the 3rd trimester [41,68]. Furthermore, the concentration of estrogens increases about fivefold even in the myometrium from early to late pregnancy [58]. Our more recent results also show that estradiol is a highly efficient predictor of GA in UA, UV, and MV (but not in amniotic fluid (AF)), while estriol was an excellent predictor in UV and in its conjugated form also in the AF [2]. The aforementioned data demonstrates increasing placental CYP19A1 activity in pregnancy. Estradiol and estrone significantly rise in UM over the course of labor but estrone remains unchanged in MV [58,65]. The increase in UV estrone may result from the change in placental metabolism that is associated with the control of parturition [65].

2.3.5. Origin of estrogens in pregnancy

The absence of fetal adrenals is associated with low estrogen levels in maternal and fetal compartments, whereas, in anencephaly, only the maternal levels are reduced (Kenny et al. [63]). The accelerating estrogen synthesis in human placental trophoblasts depends on the uptake of sulfated C19 Δ^5 steroids (originating in FZ), which is predominantly controlled by a sodium-dependent non-saturable mechanism [67] (see the Review [13]).

2.4. C19 Δ^4 steroids and their 5α/β-reduced metabolites

2.4.1. Levels of C19 Δ^4 steroids and their 5 α/β-reduced metabolites in fetal circulation

The levels of C19 Δ^4 steroids (androstenedione, testosterone) in the fetal circulation are roughly comparable with the situation in non-pregnant women [20–22,24,60,69] (Table 1) but there are strikingly lower levels of both unconjugated 5α/β-reduced androstane metabolites and their polar conjugates in the fetal blood [20] (Table 1) when compared to the situation in non-pregnant women [20,21] (Table 1), which is probably due to more rapid placental aromatization of C19 Δ^4 steroids when compared with their 5α- and 5β-reductions.

2.4.2. Umbilical arteriovenous differences, fetomaternal differences and origin of androgens in pregnancy

The levels of androstenedione, testosterone, and androsterone at delivery are higher in UA than in UV (Table 1) [36], which indicates the fetal origin of these substances, except the testosterone at week 8–18 of gestation [70]. The differences for the conjugated 5α/β-reduced androstanes are less or absent, probably due to the resistance of these catabolites to further metabolism.

2.4.3. Correlations of C19 Δ^4 steroids and their 5α/β-reduced metabolites between fetal and maternal body fluids

Androstenedione shows a strong correlation and testosterone a medium one between UA and UV, but the steroids relatively weakly correlate between UM and MV [43], and conjugated 5α/β-reduced androstanes show strong arteriovenous correlations (Table 2), which may reflect a degree of their resistance to the placental extraction.

2.4.4. Changes of C19 Δ^4 steroids in fetal blood during pregnancy and around parturition

As expected, the 16α-hydroxyandrostenedione levels in UA and UV increase in fetal and maternal body fluids concurrently with rising activities of CYP19A1 and CYP3A7 with the approaching term, and further rise after the onset of labor [2,13]. This rise suggests the fetal origin of the steroid and its mobilization by stress at the onset of labor (Ikegawa [71]).

Like androstenediol concentrations, the levels of its metabolite testosterone in UA (but not in UV and MV) negatively correlate with GA in the third trimester (Table 1), while androstenedione levels are nearly constant or slightly increase. At the same time, however, the direct estrone precursor 19-hydroxyandrostenedione rises about 7 times in fetal and maternal body fluids, which is compatible with increasing estrogen levels and rising placental CYP19A1 activity in pregnancy [2,13,24,68] (Table 1).

In contrast to DHEAS, the levels of which are about two times lower in pregnant women than in non-pregnant subjects, the concentrations of conjugated androstenediol are excessive in pregnancy and show an accelerating increase up to term [2,13] (Table 1). Declining androstenediol and testosterone levels with the approaching term may be associated with their role as key substrates being consumed for estrogen formation due to rising CYP19A1 activity in this period (Table 1). The data point to the major metabolic pathway for placental estradiol synthesis in the sequence conjugated androstenediol → androstenediol → testosterone → estradiol, which is shorter than the pathways DHEAS → DHEA → androstenedione → estrone → estradiol or DHEAS → DHEA → androstenedione → testosterone → estradiol.

2.5. Corticoids

2.5.1. Umbilical arteriovenous differences, fetomaternal differences and correlations of corticoids between body fluids in pregnancy

From midpregnancy to parturition, the cortisol, corticosterone, aldosterone, 11-deoxycortisol, and 11-deoxycorticosterone sulfate levels in UA are higher when compared to UV [52,72,73], and the cortisol levels in UA are higher in spontaneous labors compared to the induced ones [72,73], which indicates fetal origin of the substantial part of glucocorticoids in fetal circulation. There are also higher levels of mineralocorticoid precursor 11-deoxycorticosterone sulfate in UA when compared with UV [74]. The daily amounts of fetal cortisol metabolized by the placenta delivery are about 2.1 mg [37].

Cortisone dominates over cortisol in UM and correlates with cortisol in MV, while the cortisol between UM and MV does not [44,72]. Alternatively, aldosterone around parturition shows higher levels in UM than in MV [76], which may be ascribed to high levels of aldosterone precursor 11-deoxycorticosterone in the fetal circulation. Progesterone and cortisol significantly correlate in UA (week 18–41 of gestation), which indicates that the fetal cortisol is derived from the fetal progesterone [45]. On the other hand, progesterone and 11-deoxycorticosterone in UM are uncorrelated (week 18–42 of gestation) [77]. Nevertheless, sulfated 11-deoxycorticosterone strongly correlates between UA and UV [74] and the levels of 11-deoxycorticosterone and its sulfate in maternal serum significantly correlate to progesterone concentrations in MV. These results indicate that progesterone serves as a precursor even for biosynthesis of 11-deoxycorticosterone and its sulfate. Progesterone metabolite, sulfated 11-deoxycorticosterone, may enter placental trophoblasts, and the free steroid after hydrolysis is redistributed primarily to the maternal and partly also to the fetal compartment [74]. However, in the light of our recent data [13,24,31] there is a question whether the unconjugated 11-deoxycorticosterone could pass the placental syncytiotrophoblast to the maternal circulation persisting unconverted to its 3α-hydroxy- and/or 20α-dihydro-metabolites.

DHEAS in UM negatively correlates with cortisone in MV [44] and the cortisol treatment of the mother suppresses DHEAS levels in the fetal circulation [78], which may indicate a suppressive effect of the steroidogenic activity in the FZ on that in the transitional zone of the FA (TZ).

2.5.2. Changes of corticoids in fetal and maternal compartment during pregnancy and around parturition

Between weeks 18 and 30 of gestation, cortisol, cortisone, and 11-deoxycorticosterone in fetal and maternal circulations are almost independent of GA [44,45,77], but during labor, cortisol levels rise in the myometrium and UM [58] due to increasing stress. Narasaka et al. (see the Review [13]) demonstrated the onset of cortisol production in the TZ after week 23 of gestation. In contrast to almost constant cortisol levels in the fetal circulation, 11-deoxycorticosterone sulfate and progesterone concentrations increase (week 18–42 of gestation) as the term nears, which is compatible with the role of fetal progesterone as a precursor for production of 11-deoxycorticosterone and its sulfate [77].

2.5.3. Origin of corticoids in pregnancy

After week 23 of gestation (see the Review [13]), the fetus most probably synthesizes cortisol and less amounts of cortisone from the fetal progesterone [45], while most of the fetal cortisone originates in placenta during the transplacental passage from maternal cortisol being converted by type 2 11β-hydroxysteroid dehydrogenase (HSD11B2) [44,72,75]. In contrast to fetal cortisone,

aldosterone primarily originates from the metabolite of the fetal progesterone (11-deoxycorticosterone) [76].

2.6. 5α/β-reduced pregnane steroids

2.6.1. Levels of 5α/β-reduced pregnane in fetal body fluids and tissues

In the fetal and maternal body fluids as well as in non-pregnant women, the sulfated forms of 5α/β-reduced pregnane steroids dominate over their unconjugated counterparts [19,20,24,35] (Tables 1 and 3) and in both cases, pregnancy levels exceed the corresponding concentrations in non-pregnant women in the follicular menstrual phase by 1–3 orders of magnitude [19,20,24,79–81].

5α/β-Reduced pregnane steroids are also present in high concentrations in various fetal tissues. For instance, the levels of unconjugated pregnanolone isomers in fetal tissues displayed as mean (maximum) are as follows (pmol/g): Allopregnanolone: brain 35 (60), placenta 53 (41), skin 69 (116), lung 82 (151), liver 9 (19), kidney 75 (321), intestine 85 (145), myometrium 30 (89); Isopregnanolone: brain 211 (494), placenta 186 (308), skin 50 (126), lung 362 (1009), liver 107 (528), kidney 368 (1321), intestine 148 (434), myometrium 63 (220); Pregnanolone: brain 50 (170), placenta 25 (53), skin 0 (0), lung 3 (6), liver 412 (824), kidney 129 (214), intestine 314 (594), myometrium 31 (92) [16–18].

2.6.2. Umbilical arteriovenous differences and fetomaternal differences and correlations of 5α/β-reduced pregnane steroids between body fluids in pregnancy

Fetal liver converts the progesterone to its 5α/β-reduced metabolites while placenta converts the progesterone to the 5α-reduced ones only. The 5α/β-reduced pregnanes are readily conjugated in the liver (for review [13]). Although Mickan and Zander [35] reported similar levels in UA and UV for isopregnanolone, our data for unconjugated isopregnanolone show its higher levels in UA than in UV [24] (Table 1), which indicates fetal origin of this steroid. Pregnanolone is more effectively eliminated from the fetal compartment than the 5α-isomers [35] probably due to highest avidity for sulfation from the pregnanolone isomers [19]. Whereas the 5α-pregnanolone isomers (allopregnanolone and isopregnanolone) show less differences between their levels in fetal and maternal blood due to broad 5α-reductase (SRD5A) expression in fetal and maternal compartments, the levels of the 5β-isomer pregnanolone are higher in the fetal circulation due to the specific expression of 5β-reductase (AKR1D1) in the fetal liver (see the Review [13]) [24,35] (Table 1).

The levels of unconjugated 3β-pregnanolone isomers (isopregnanolone and epipregnanolone) at normal labor are significantly higher in the UM than in the MV, while the 3α-isomers displayed comparable values in these body fluids. In general, there is a higher proportion of 3β- and 5β-pregnanolones in the fetal circulation when compared to the maternal one [2,13,24,81] (Table 1). The ratios of conjugated to unconjugated pregnanolones are consistently higher in MV when compared to UM [2,13,81]. Given their abundance of GABAergic 3α-pregnanolones and turnaround of their GABAergic effect by sulfation [82], pregnanolone isomers and their polar conjugates have a role in the onset of human labor [2,13,24,81]. Both unconjugated pregnanolone isomers (allopregnanolone, isopregnanolone, pregnanolone, epipregnanolone) and unconjugated pregnanediols strongly correlate between UA and UV, while their polar conjugates show even stronger arteriovenous correlations (Table 2). Allopregnanolone also strongly correlate between UA and MV, which also indicates similar activities of SRD5A in maternal and fetal compartments [38].

2.6.3. Changes of 5α/β-reduced pregnane and androstane steroids in fetal blood during pregnancy and around parturition

Conjugated pregnanolones positively correlate with GA but less strongly than the conjugated Δ^5 steroids [2]. Of the 5α/β-reduced androstane steroids, conjugated epiandrosterone is an excellent predictor of GA possibly due to its higher stability in body fluids as compared to its C19 precursor androstenedione, the levels of which are unrelated to GA [2].

2.7. Gender differences in steroid levels

Various authors who investigated gender differences in a number of fetal steroids (Preg17, progesterone, E1, E2, E3) found insignificant minor differences [40,49,54,58,59]. The only period during the pregnancy in which the fetal gender notably influences the levels of fetal androgens is the early pregnancy (weeks 8–18 of gestation). In this period, testosterone shows higher levels in cord serum in male fetuses when compared to the serum of female ones, maternal serum and serum from newborns of both genders. During early pregnancy, testosterone concentrations in the testicular tissue are manifestly higher when compared to the serum levels, which demonstrates a pronounced testosterone production in the fetal testes in this stage and points to key role of testosterone in human sexual differentiation [70].

3. Changes in steroidogenesis during late pregnancy

3.1. Steroid ratios reflecting the activity of C17-hydroxylase, C17,20 lyase (CYP17A1)

Due to negligible conversion of C21 Δ^4 steroids into their C19 counterparts by CYP17A1 [83], our current unpublished data summarizing product-to-precursor ratios associated with the CYP17A1 activity (Table 3) does not take into consideration the ratios for the Δ^4 steroids. Although the concentrations of C19 Δ^5 steroids are comparable with the situation in non-pregnant women, the levels of C21 Δ^5 steroids are excessive in the fetal circulation and still substantially elevated in the maternal one [84], which indicates limited CYP17A1 activity in the FZ even for the C21 Δ^5 steroids.

The Δ^5 steroids are readily metabolized by placental enzymes and their changes in UV may rather reflect the changing placental steroidogenesis than the changing CYP17A1 activity in the fetal adrenal. Therefore, our current unpublished data (Table 3) are not consistent as concerns the product-to-precursor ratios related to CYP17A1 activities in UA and UV. However, there is a consistent result concerning absent AVD in these ratios, which is compatible with negligible placental CYP17A1 activity (for review [13]).

3.2. Steroid ratios reflecting the activities of 3β-hydroxysteroid dehydrogenase (HSD3B)

The progesterone/pregnenolone ratio in UV showing independence on GA is in all probability dominantly under the control of the placental HSD3B1 activity being independent of GA (for review [13]). Table 3 shows that the steroid ratios related to HSD3B activities are pronouncedly higher in UV than in UA, which demonstrates the primarily placental origin of the fetal Δ^4 steroids. Therefore, while the pregnenolone to progesterone conversion, at least in the third trimester, is actually unrelated to GA, other substances on leaving the placenta surprisingly show escalating ratios of the Δ^4 steroids to the Δ^5 ones with advancing gestation.

The onset of cortisol production in the TZ initiates after week 23 of gestation, but very premature newborns (week 24–33 of

gestation) exhibit neither reduced 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) activity nor lower steroid 11β-hydroxylase (CYP11B1) activity [86] (for review [13]). Therefore, whereas the ratios of Preg17 to Prog17 and the ratios of 11-deoxycortisol to cortisol are uncorrelated with cortisol levels, the observed lower cortisol levels in the fetal blood at delivery compared to the situation postpartum is linked to placental HSD11B2 activity converting the cortisol of both maternal and fetal origin to cortisone and not to the altered fetal cortisol production.

Both HSD3B isoforms catalyze the oxidative conversion of Δ^5 steroids to their Δ^4 counterparts. The onset of type 2 HSD3B (HSD3B2) activity in the TZ and DZ was reported from the week 23 of gestation. As was already mentioned, HSD3B2 is necessary for the corticoid production in the fetus and maturation of fetal lung (for review [2]) and monitoring the HSD3B activities via the product to precursor ratios related to HSD3B activities may be of importance. Maruyama et al. [85] showed low Δ^4/Δ^5 steroid ratios in the blood of women with intrauterine growth retardation (IUGR) pregnancies and suggested impaired HSD3B1 activity in these patients.

3.3. Steroid ratios reflecting the aromatase (CYP19A1) activity

Rising CRH levels near term stimulate estrogen biosynthesis in the human placental trophoblasts. Furthermore, while adult liver exhibits little CYP19A1 activity, the fetal one also extensively aromatizes the C19 steroids. The CYP19A1 activity in the fetal hepatocytes appears to be further up regulated by increasing production of glucocorticoids in the TZ (for review [2]). Our current unpublished data demonstrate a consistent rise in the values of steroid ratios reflecting the CYP19A1 activity (estrone/androstenedione, estradiol/testosterone) and significantly higher values of these ratios in UV compared to UA (Table 3), which is compatible with data from others who demonstrate escalating placental CYP19A1 activity with advancing GA, which weakens near term (for review [13]).

3.4. Steroid ratios reflecting the 16α-hydroxylase (CYP3A7) activity

As expected, there is higher Preg16α/pregnenolone ratio in the UA (Table 3). Alternatively, the 16α-hydroxy-progesterone/progesterone ratio does not differ between UA and UV, and for the DHEA and androstenedione there are higher 16α-hydroxy-/16-deoxysteroid ratios in UV. However, not only these ratios but also the levels of 16α-hydroxy-DHEA and 16α-hydroxy-DHEAC are higher in the UV than in UV (Table 1). The explanation for this finding might be the ability of placenta to preferentially process 16-deoxy-steroids over 16α-hydroxy-steroids, the majority of which are returned unconverted to the fetal compartment. This concept is consistent with the reports of Cantineau et al. [87] and Othman and Oakey [88] demonstrating that 16α-hydroxy-metabolites of C19 steroids are only poor substrates for the placental CYP19A1 in contrast to the corresponding 16-deoxy-steroids [88].

16α-Hydroxylation is provided by CYP3A7, which is specifically and pronouncedly expressed in the microsomal fraction from the fetal/neonatal liver. CYP3A7 converts the DHEA to 16α-hydroxy-DHEA and 7β-hydroxy-DHEA. Besides the fetal liver, it is also active in the FA (for review [13]). Our present data show that only Preg16α/pregnenolone, 16α-hydroxyestrone/estrone and estriol/estradiol ratios are independent of GA, while the remaining ratios reflecting the CYP3A7 activity rise with advancing GA (Table 3). Furthermore, almost all 16α-hydroxy-steroids exhibit a significantly increasing trend with advancing gestation (Table 1). These findings for 16α-hydroxy-estrogen/16-deoxy-estrogen ratios are consistent with the concurrent increase of the CYP19A1 in the placenta and CYP3A7 in the fetal liver as the rising CYP3A7 activity provides a protection against hyperestrogenization by 16α-hydroxylation of estrogen precursors and estrogens.

3.5. Steroid ratios reflecting the 5α-reductase (SRD5A) activities

The 5α-dihydroprogesterone/progesterone ratio reflecting the (SRD5A activities is lower in UV, but the 5α,20α-tetrahydro-progesterone/Prog20α ratio is slightly, albeit significantly higher in UV possibly due to preferential conversion of Prog20α to progesterone in the placental tissues in close contact with the fetal circulation (for review [24]). Therefore, the lower values of 5α-dihydroprogesterone/progesterone ratios in UV point to the fetal liver (and not the placenta) as the key source of at least fetal 5α-reduced progesterone metabolites.

The SRD5A1 expression is also four times higher in the fetal liver compared to the adult one, which points to the major role of the fetal liver in the synthesis of peripheral neuroactive and neuroprotective steroids (for review [13]). Placental SRD5A catalyze the synthesis of 5α-reduced steroids. Some of these substances modulate ionotropic receptors and exert neuroprotective effects in the fetus. Both 5α-reductase isoforms (type 1 (SRD5A1) and type 2 (SRD5A2)) show an increasing expression with advancing gestation (for review [13]). Alternatively, our current unpublished data covering the third trimester show that the steroid ratios reflecting the SRD5A activities in the fetal periphery are independent of GA (Table 3). Nevertheless, the SRD5A1 expression in the human brain is highest compared to any other human tissue, and the SRD5A1 expression in the fetal brain is seven times higher than in the adult one [33]. This data indicates an essential role of the enzyme in the fetal CNS, which is associated with neuroprotection (for review [89]).

3.6. Steroid ratios reflecting 5β-reductase (AKR1D1) activity

The progesterone metabolite 5β-dihydroprogesterone is a potent tocolytic agent. The 5β-reduced progesterone metabolites in pregnancy persistently help sustain it by binding to nuclear pregnane X receptors and progesterone receptors. Furthermore, the acute in vitro treatment with 5β-dihydroprogesterone causes rapid uterine relaxation that is not mediated by nuclear receptors. AKR1D1 is primarily expressed in the liver. Nevertheless, in the placenta and myometrium, the relative expression of AKR1D1 at labor drops by about two-fold and 10-fold, respectively (for review [13]). The aforementioned indicate physiological relevance of 5β-reduced progesterone metabolites in the sustaining of human pregnancy.

Table 3 shows that the 5β-dihydroprogesterone/progesterone ratio is lower in UV while the 5β,20α-tetrahydroprogesterone/Prog20α ratio is slightly but significantly higher in UV. The explanation for the latter finding may be analogous to the higher 5α,20α-tetrahydroprogesterone/Prog20α ratio in UA as discussed in the previous section. The lower values of 5β-dihydroprogesterone/progesterone ratios in UV also point to the fetal liver as a tissue primarily producing the fetal 5β-reduced progesterone metabolites and at least considerable amounts of the maternal ones.

The steroid ratios reflecting the AKR1D1 activity (5β-dihydroprogesterone/progesterone and 5β,20α-tetrahydroprogesterone/progesterone) and almost all 5β-reduced pregnane metabolites gradually decrease with advancing GA (Tables 1 and 3), which is compatible with the data in the literature (including ours) demonstrating an attenuation of AKR1D1 activity with the approaching term (for review [13]). Some data also indicate that substrate inhibition of AKR1D1 by Δ^4 steroids and estrogens might contribute to the induction of labor by estrogens [90]. The presence of other Δ^4 steroids, particularly 11-deoxy-corticosterone

and androstenedione is suggested to decrease the synthesis of 5β-dihydroprogesterone by AKR1D1. Whereas the androstenedione levels are slightly elevated during labor, the levels of its aromatase product estrone are excessive in this period [2] (Table 1). Due to permissive ligand binding pocket of AKR1D1, it is likely that steroids, which do not function as substrates for the enzyme, including estrogens, may be its inhibitors [90]. This data may be of importance with regard to the stability of pregnancy and initiation of human parturition (for review [13]).

3.7. Steroid ratios reflecting the activities of pluripotent enzyme isoforms from the 17β-hydroxysteroid dehydrogenase (HSD17B) and aldo-keto reductase family 1, member C (AKR1C)

The enzymes catalyzing reversible C-3, C-17 and C-20 oxido-reductive inter-conversions belong to either the short-chain dehydrogenases/reductases (HSD17B) or the family 1, member C aldo-keto reductases (AKR1C). Various isoforms of the aforementioned enzymes preferring either oxidative or reductive direction are widely but differentially expressed in placenta and fetal tissues like adrenal, liver, kidney lung and brain [13,33].

Our current unpublished data (Table 3) show that the values of steroid ratios reflecting the balance between activities of pluripotent reductive isoforms of HSD17B and AKR1C and pluripotent oxidative ones of HSD17B (3α-hydroxy-steroids/3-oxo-steroids, 3α-hydroxy-steroids/3β-hydroxy-steroids, 17β-hydroxy-steroids/17-oxo-steroids and 20α-hydroxy-steroids/20-oxo-steroids are generally lower in UV compared to UA, which points to the predominantly reductive status of the steroids with hydroxy-/oxo-groups in the C3, C17 and C20 positions in UA (driving the blood from the fetus to the placenta) and to the oxidative one in UV (driving the blood from placenta to the fetus). Placenta preferentially expresses more oxidative placental isoforms of HSD17B in close contact with the fetal blood, while the reductive placental isoforms of HSD17B and AKR1C are predominantly expressed in proximity to the maternal circulation [13]. Thus the reductive isoforms in the fetus convert a part of the 3-oxo-5α/β-reduced pregnanes to their GABAergic neuroactive and neuroprotective 3α-hydroxy-counterparts) and thus partly revert the unfavorable status of pregnane steroids secreted by placenta in their inactive 3-oxo-forms. On the other hand, these reductive fetal enzyme isoforms also convert a part of the active progesterone to the inactive 20α-dihydroprogesterone and a part of the inactive estrone to the active estradiol.

As for the higher values of the allopregnanolone/isopregnanolone and 5α-pregnane-3β,20α-diol/isopregnanolone ratios and higher isopregnanolone levels UV, these may result due to activities of some oxidative HSD17B isoforms in the fetus converting not only the 3α-hydroxyl groups to the 3-oxo-groups, but also the 3-oxo-groups up to the 3β-hydroxyl groups (Tables 1 and 3).

With the exception of some 3α-hydroxy-steroid/3-oxo-steroid ratios, the steroid ratios reflecting the activities of pluripotent HSD17B and AKR1C exhibit evidently increasing trend toward production of 3-/17-/20-oxo steroids at the expense of 3α-/17β-/20α-hydroxy-steroids with advancing GA (Table 3). This trend weakens in the sequence of C17, C3, and C20 steroid positions. The finding is of great physiological and pathophysiological importance as the conversion of oxo- to hydroxy-group is decisive for bioactivity of several important steroid hormones that are effective in human pregnancy. Our results show that there is a tendency to higher placental production of active progestogen but lower production of active estrogen and active GABAergic steroids with advancing GA in the proximity of the fetal circulation.

3.8. Balance between conjugated and unconjugated steroids

Steroid conjugates in fetal circulation originate in the fetal tissues and cannot be of placental origin due to their high STS placental expression and activity [33] (for review [13]). Their circulating levels in the fetus are 1–3 orders of magnitude higher when compared to their unconjugated counterparts [34] (Table 4).

The ratios of steroid polar conjugates to unconjugated steroids (C/U) reflecting a balance between activities of steroid sulfotransferases and glucuronosyltransferases on the one hand and activities of steroid sulfatases and glucuronidases on the other hand, show an increasing trend with advancing gestation [2,13,91] (Table 4). Cole et al. [92] report analogous results even for inorganic sulfate. SULT2A1 displaying reactivity toward 3α/β-hydroxy-steroids, estrogens, and 17β-hydroxy-group of androgens is highly expressed in the adrenal cortex and relatively abundantly in the liver. On the other hand, the expression and activity of placental STS (being independent of the substrate concentration and GA) explicitly outweighs its expression and activity in other tissues (for review [13]).

Most steroids display higher C/U values in UV than in UA, like most Δ^5 steroids, almost all 5α/β-reduced – pregnane and androstane steroids, and 20α-dihydroprogesterone (Table 4), which indicate relative resistance to placental hydrolysis of their conjugated forms at more rapid metabolism of their unconjugated ones. Alternatively, the lower C/U in UV for pregnenolone, 16α-hydroxy-DHEA, Prog17, estrogens (estrone, estradiol, and estriol) (Table 4) indicate higher avidity to placental hydrolysis for their conjugated forms at slower placental metabolism of their unconjugated ones. Only the C/U for 16-deoxy-estrogens (estrone and estradiol) decrease with advancing GA (Table 4), which might be explained by differently changing activities of enzyme isoforms catalyzing steroid conjugation, like the estrogen preferring sulfotransferase (SULT1E1), SULT2A1 catalyzing steroid sulfation (including estrogens), sulfotransferase family cytosolic 2B member 1 isoform (SULT2B1) catalyzing the sulfation of non-estrogenic steroids and unspecific glucuronosyltransferases, such as liver UDP-glucuronosyltransferase 2B7 (UGT2B7).

The balance between free steroids and their conjugates may be crucial for the regulation of steroid biological activity. The 5α/β-reduced progesterone metabolites with a hydroxy-group in the 3α-position positively modulate the $GABA_A$-r while the sulfates of 5α/β-reduced progesterone metabolites operate in the opposite way. Sulfation may also decrease the concentrations of unconjugated neuroactive steroids, the polarity of which is more favorable for crossing the blood–brain barrier. On the other hand, the conjugation is a prerequisite for the activity of 3α/β-hydroxy-5α/β-reduced pregnanes on neuroexcitatory N-methyl-D-aspartate receptors (NMDA-r) showing positive and negative modulation for the 5α- and 5β-isomers, respectively. Finally, the sulfation may also facilitate steroid transport by the circulation. In general, the sulfation shifts the biological activity toward induction of labor catabolizing the steroids, which provide uterine quiescence. Steroid sulfates like the DHEAS also stimulate phospholipase activity and may be involved in the regulatory mechanism for prostaglandin synthesis in the amniotic membrane (for review [13]).

4. Physiological relevance of endogenous steroids in the fetal nervous system

Since the physiological relevance of steroids modulating the ligand gated ion channels in the fetus is frequently unclear, we attempted to derive this information from a combination of pharmacological characteristics found in the literature, knowledge from

the gene expression databases, and published metabolomic data (including our own).

4.1. Steroids in fetal brain

Steroids predominantly penetrate the brain–blood barrier (BBB) according to their lipophilicity and reach generally different and frequently higher concentrations in brain tissue when compared to the circulating levels. For instance, the brain concentrations of several steroids and steroid polar conjugates in human brain as derived from the results of various authors (including us) and adjusted for the week 33–37 of gestation (based on our current unpublished data for UA) are as follows (pmol/g, mean (maximum)): Pregnenolone 31 (65) [16], PregS 130 (425) [16], DHEA 52 [20,93–95], DHEAS 34 [20,93,95,96], progesterone 766 (2868) [16], testosterone 2.1 [20,93,97,98], androsterone 1.1 [20,97], estradiol 0.76 [99], allopregnanolone 27 (47) [16], isopregnanolone 178 (419) [16], pregnanolone 31 (106) [16].

4.2. Physiological relevance of fetal steroids exerting non-genomic effects

4.2.1. Fetal steroids and GABA receptors

Despite the unfavorable penetrability through the BBB, PregS reaches concentrations, which appears to be relevant for inhibition the vesicular release of GABA by diminishing the frequency of inhibitory postsynaptic currents (IPSCs) in hippocampal pyramidal neurons (IPSCs) [100]. From the positive $GABA_A$-r modulators, the pregnanolone [101,102] and allopregnanolone [103] levels in the fetal brain are most probably sufficient to modulate various $GABA_A$-r subtypes.

4.2.2. Fetal steroids and glycine receptors

In respect of the limited penetrability of PregS and DHEAS through the BBB, their concentrations on the peripheral level but not in the brain tissue might reach physiological relevance for negative modulation of glycine receptors (GLR) [104], while the allopregnanolone levels are in all probability sufficient to exert neuroprotective effect by a positive modulation of GLR [18,105] in the CNS. On the other hand, progesterone might act as a negative modulator of GLR in both fetal CNS and periphery [104].

4.2.3. Fetal steroids and NMDA receptors

In respect of their pharmacological characteristics, the positive NMDA-r modulators, like the conjugated 20α-dihydropregnenolone, PregS and DHEAS at concentrations common in the fetal brain and circulation, might attain relevance in the periphery but hardly in the CNS [106,107]. On the other hand, estradiol probably exerts protective effect in the fetal brain via influencing the NMDA-r [108].

4.2.4. Fetal steroids and AMPA/kainate receptors

Some subtypes of 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA)/kainate receptors show substantially higher expressions in the fetal brain when compared to the adult one [33]. PregS probably does not reach relevant concentrations for influencing AMPA/kainate receptors in the fetal CNS but the neuroprotective effect of PregS via these receptors may be relevant at the peripheral level [109,110]. On the other hand, allopregnanolone may serve as a neuroprotective negative modulator of AMPA/kainate receptors [111] in the CNS. In contrast to allopregnanolone and PregS, functioning as neuroprotective substances on AMPA/kainate receptors, estradiol is probably neuroexcitatory at these receptors and its concentrations in the fetal CNS might potentiate kainate-induced currents [112]. Therefore, the previously mentioned anti-estrogenic mechanisms in the fetus also exert a neuroprotective effect. Similarly, a potent glucocorticoid dexamethasone stimulates the neuronal expression of glutamate, kainate 2 receptor (GRIK2) and kainate-induced currents in the mouse hippocampus [113]. Therefore, the previously mentioned placental conversion of maternal cortisol to inactive cortisone might exert the neuroprotective effect in the fetus as well.

4.2.5. Fetal steroids and transient receptor potential channels

PregS at concentrations common in the fetal circulation functions as a rapid and reversible positive modulator of transient receptor potential cation channels subfamily M member 3 (TRPM3) in pancreatic β-cells. The activation of TRPM3 causes calcium influx and subsequent insulin release. Alternatively, progesterone at concentrations that are common for the fetal circulation (10 nM to 10 μM) may effectively suppress the PregS evoked TRPM3 activity [114]. Whereas the TRPM3 modulates glucose homeostasis, the balance between the antagonistic steroids with excessive abundance, which is specific for the fetus, may be important in various pathologies connected with glucose tolerance and/or insulin insensitivity like undesirable fetal programming or gestational diabetes in mothers. Interestingly, life periods with elevated levels of circulating steroids like pregnancy, puberty or even luteal menstrual phase are frequently associated with decreased insulin sensitivity (for review [115]).

In contrast to neuroexcitatory effect on TRPM3, fetal progesterone attains the concentrations permitting its functioning as a neuroinhibitory and pregnancy stabilizing substance on various isoforms of transition receptor potential channels (TRP), which are expressed in pregnancy-related tissues including the vascular remodeling in the fetus via channels of the TRPC family [114,116–121].

PregS at the levels common in the fetal circulation may also attain the relevance as a neuroinhibitory substance on capsaicin receptors (TRP subfamily V member 1, TRPV1) [122]. TRPV1 are predominantly distributed in the nociceptive neurons of the peripheral nervous system and are involved in the transmission and modulation of pain [123,124]. Therefore, the excessive concentrations of PregS in the periphery might lessen the impact of the painful stimuli in fetuses and newborns.

4.2.6. Fetal steroids and low type voltage gated calcium channels

Fetal steroids may be physiologically relevant in the modulation of low-type voltage gated calcium channels (L-type VGCC) in various brain tissues. The negative L-type VGCC modulators like pregnenolone, PregS and estrogens may operate as potent neuroprotective substances [125,126] in contrast to their neuroexcitatory effects on other ligand-gated ion channels. Alternatively, in contrast to allopregnanolone neuroinhibitory effect on $GABA_A$-r and AMPA/kainate receptors, allopregnanolone concentrations in the fetal CNS permit an effective amplification of intracellular calcium influx into the fetal hypothalamic neurons [127,128].

4.2.7. Fetal steroids and serotonin receptors

The circulating levels of progesterone, DHEAS, and PregS levels are sufficient to exert relevant physiological effects [129–131] at contractile serotonin receptors (5HT-r), which are expressed in pregnant human myometrium [132]. This tissue is crucial for the stability of pregnancy. On the type 3 5HT-r progesterone and estradiol are effective at 1 μM and 300 nM, respectively [133]. Wetzel et al. [133] suggested that pregnancy nausea may be linked to progesterone and estradiol antagonism at these receptors.

5. Steroid metabolome in the fetus and fetal programming

Fetal androgens, glucocorticoids and possibly also the GABAergic steroids may participate in the fetal programming of HPA

and HPG axes, which is critical for the occurrence of endocrine disturbances in further stages of human life like female hyperandrogenism, polycystic ovary syndrome (PCOS), insulin insensitivity, or neuropsychiatric disorders.

Some authors [8] suggest that activation of $GABA_A$-r in gonadotropin-releasing hormone (GnRH) producing cells by GABAergic steroids may participate in the development of predisposition to PCOS in hyperandrogenized female fetuses, while others [7] demonstrate that instead of the $GABA_A$-r, the AMPA/kainate receptors (which are overexpressed in the fetal CNS [33]) arrange gender differentiation in the hypothalamic ventromedial nucleus and estradiol (originating in the fetal brain from the testosterone of peripheral origin) mediates the masculinization, induced in the investigated animals.

In early gestation, the hyperandrogenization of female fetuses appears to be without negative consequences, while the hyperandrogenization in late gestation may induce delayed menarche, increased sensitivity to androgens in this period and increased HPA activity in mothers [11]. While the prenatal hyperandrogenization induces reproductive disturbances similar to PCOS in female animals only [9], the impaired insulin sensitivity occurs in both sexes [134]. Moreover, the glucocorticoid excess induced by glucocorticoid treatment or prenatal stress may have serious consequences in adulthood, such as increased HPA activity, hypertension, hyperglycemia, anxiety and even inheritance of these disturbances into the further generation [10]. Masuyama and Hiramatsu [135] who evaluated the role of constitutive androstane receptor (CAR) in the development of insulin resistance in pregnancy using a mouse model demonstrated that estradiol and progesterone may also restrain CAR-mediated signaling at levels common in pregnant women.

The aforementioned data show that the quantification of steroid metabolome in umbilical blood at labor might be utilized for predicting fertility disorders in the subsequent stages of life in women and for prediction of insulin insensitivity in both genders.

6. Conclusive remarks

This review focused on steroid profiling in human fetuses and newborns and the role of the steroids in the physiology and pathophysiology of human pregnancy. Particular attention was paid to the physiological relevance of steroids-influencing activities of the central and peripheral nervous systems with regard to their concentrations in the fetus. We discussed the possible roles of abundant fetal steroids exhibiting non-genomic effects like pregnenolone sulfate, progesterone and allopregnanolone in the development of gestational diabetes and undesirable fetal programming and neuroprotective effects of the steroids. The physiological relevance of increasing placental progesterone synthesis, the declining production of tocolytic 5β-pregnane steroids and rising activity of steroid sulfotransferases with advancing GA in the third trimester of pregnancy was discussed.

An alternative mechanism was mentioned for progesterone synthesis from the fetal PregS that is closely associated with the distribution of placental oxidoreductases. An increasing trend in the human fetus was accentuated toward production of 3-oxo-(3β-hydroxy-), 17-oxo, and 20-oxo-groups on the expense of their 3α-hydroxy-, 17β-hydroxy-, and 20α-hydroxy-counterparts in the fetus and therefore a tendency toward higher production of active progestogen, but lower production of active estrogen and GABAergic steroids with advancing gestation.

We also sketched an anti-estrogenic mechanism in the fetus that is based on increasing 16α-hydroxylation and sulfation of estrogens and their precursors in cooperation with the increasing activity of oxidative HSD17B isoforms in the placenta and fetal liver with advancing gestation. These mechanisms may protect the fetus from hyperestrogenization induced by rising placental CYP19A1 activity with the approaching term.

Finally, a potential utilization of steroid metabolomics was described in fetal and newborn circulation for predicting the occurrence of steroid endocrinopathies in subsequent stages of human life.

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