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## Metabolism of Progesterone in the Newborn

CH. LAURITZEN

The fetus does not contribute significantly to the production of progesterone and other gestagens originating from the placenta in pregnancy (CASSMER, 1959; DICZFALUSY and TRÖEN, 1961). Greater amounts of progesterone flow from the placenta to the fetus, where they are partly metabolized (RUNNEBAUM and ZANDER, 1962; HARBERT et al., 1964; ZANDER, 1964; PALMER et al., 1952). Some of these steroids are excreted in the urine of the newborn in the first days of life. Principally, however, the fetus and the newborn may be able to produce progesterone of its own (FORBES, 1955; DAVIS and PLOTZ, 1957). Not much is known about the conditions of pregnane production and metabolism in the newborn. We have therefore investigated the excretion of progesterone, progesterols and of some pregnene and pregnane derivatives and metabolites in the urine of the first days of life.

### *Material and methods*

The investigations were performed in 55 newborns of both sexes. The urines were collected in coloplast bags. The determination of progesterone and the progesterols (20 $\alpha$ - and 20 $\beta$ -hydroxy-pregn-4-ene-3-one) was done according to SCHUBERT, using the sulfuric acid reaction as described by ZAFFARONI. Determinations of pregnenolone (3 $\beta$ -hydroxy-pregn-5-en-20-one) and 16 $\alpha$ -hydroxy-pregnenolone were done according to the methods of SHACKLETON and MITCHELL (1967), the determination of pregnanediol (3 $\alpha$ ,20 $\alpha$ -dihydroxy-5 $\beta$ -pregnane) and of pregnanolone (3 $\alpha$ -hydroxy-5 $\beta$ -pregnane-20-one) was performed according to the method of SCHNEIDER and SZEREDAY (1965).

### *Results*

Progesterone and progesterol were found in 19 out of 27 determinations in the first two days' urine. The newborns excrete progesterone in a concentration of 0–40  $\mu\text{g}$  per 24-hour urine. Progesterol-20 $\alpha$  and -20 $\beta$  are excreted in amounts between 0 and 48  $\mu\text{g}$ . The excretion of the pregnanes is highest in the first two days and declines thereafter to barely detectable levels (Table I). Pregnanediol is excreted in a rate of 40–200  $\mu\text{g}/24$ -hour urine. The excretion is also highest in the first days of life. In the following days values between 50 and 110  $\mu\text{g}$  are found (Table II). The level of pregnanolone in the urine lies between 150 and 475  $\mu\text{g}/24$ -hour urine with a rather constant excretion in the first week (Table III). Administration of ACTH (8 IU/day) caused

Table I  
Excretion of progesterone and progesterol in newborn urines of the first days of life

Name, sex	1st day of life		2nd day of life		3rd day of life	
	progesterone in 24 h urine	progesterone/ 20 $\alpha$ and 20 $\beta$ progesterol in 24 h urine ratio	progesterone in 24 h urine	progesterone/ 20 $\alpha$ and 20 $\beta$ progesterol in 24 h urine ratio	progesterone in 24 h urine	progesterone/ 20 $\alpha$ and 20 $\beta$ progesterol in 24 h urine ratio
Bo. ♀	34.0 mg	0.99	23.0 mg	0.47	-	-
Un. ♂	28.0 mg	1.32	17.9 mg	0.84	-	-
Po. ♂	20.8 mg	2.66	18.4 mg	2.59	-	-
Gr. ♂	8.6 mg	0.76	6.5 mg	1.05	-	-
Kz. ♂	28.3 mg	-	20.4 mg	1.06	-	-
Ja. ♂	40.3 mg	3.07	37.4 mg	3.56	10.9 mg	5.6 mg 1.99
Ri. ♂	13.0 mg	0.38	28.2 mg	1.28	-	-
Sch. ♂	14.5 mg	1.38	38.2 mg	3.41	-	-
La. ♂	9.5 mg	-	13.9 mg	-	-	-
Pe. ♂	17.0 mg	-	-	-	10.6 mg	5.9 mg 1.80
Mean	21.4 mg		22.6 mg		10.8 mg	5.7 mg
±	11.0 mg		12.6 mg		13.2 mg	

Table II  
Excretion of pregnanediol in 24 h urine of newborns

Sex	Weight (g)	Urine (ml), day of life						Excretion of pregnanediol (mg/24 h urine), day of life						Mean of the 6 days
		1st	2nd	3rd	4th	5th	6th	1st	2nd	3rd	4th	5th	6th	
♂	2890	65	72	130	133	210	230	65.5	58.0	56.1	48.5	41.1	48.8	53.0
♂	4070	41	21	52	110	135	155	201.5	65.5	140.5	101.0	93.5	110.7	118.8
♀	3120	17	33	22	90	120	135	145.9	143.0	62.0	137.5	101.1	108.7	116.4
♀	3760	56	33	120	210	205	190	96.5	50.5	78.5	64.2	41.1	51.0	73.8
Mean =							127.4	78.8	84.3	87.8	69.2	79.8	88.0	

Table III  
Excretion of pregnanalone in 24 h urine of newborns

Sex	Weight (g)	Urine (ml), day of life						Excretion of pregnanalone (mg/24 h urine), day of life						Means of the days 1-6 14-16	
		1st	2nd	3rd	4th	5th	6th	1st	2nd	3rd	4th	5th	6th		
♂	2890	65	72	130	133	210	230	252.5	300.0	380.5	312.5	300.0	350.0	315.9	244
♂	4070	41	21	52	110	135	155	475.0	275.0	325.0	385.0	375.0	286.0	353.5	270.2
♀	3120	17	33	22	90	120	135	170.0	285.0	152.0	465.0	350.0	395.9	319.5	251.1
♀	3760	56	33	120	210	205	190	437.5	167.5	215.0	325.0	280.0	334.0	293.2	225.5
Mean =							358.5	256.9	265.6	371.9	326.3	341.2	320.8	246.9	(69-320)

Table IV

Excretion of pregnanediol and pregnanolone in the urine of the newborns before and following injection of 8 IU ACTH per day

Sex	Weight (g)	Urine (ml)						Age of newborn (days)	Excretion (mg) before ACTH			Excretion (mg) during ACTH (8 IU/day)			Significance
		1st	2nd	3rd	4th	5th	6th		day of life: 1st 2nd 3rd			4th	5th	6th	
♂	3710	290	245	340	335	220	405	14	pregnanediol 37.4	93.5	63.6	134.6	172.0	140.3	p 0.05
									pregnanolone 100.0	185.0	190.0	340.0	285.0	285.0	p 0.05
♀	4020	60	85	100	205	280	310	4	pregnanediol 65.5	119.7	168.3	191.8	93.5	74.5	∅
									pregnanolone 250.0	384.0	375.0	487.0	370.0	295.0	∅
♀	3670	40	100	150	190	265	280	4	pregnanediol 80.2	116.9	67.3	74.8	140.3	196.5	p 0.05
									pregnanolone 150.0	272.0	200.0	285.0	442.0	465.0	p 0.05
♂	3330	28	75	53	150	150	245	4	pregnanediol 114.3	187.0	193.8	280.5	249.6	287.0	p 0.05
									pregnanolone 475.0	575.0	582.0	750.0	780.0	930.0	p 0.05
♀	4100	295	280	330	320	290	330	14	pregnanediol 84.2	123.4	129.0	140.2	179.5	195.8	p 0.05
									pregnanolone 220.0	321.0	368.0	420.0	570.0	505.0	p 0.05
♂	3450	150	190	230	275	270	225	14	pregnanediol 67.3	63.5	61.8	61.8	82.3	91.6	∅
									pregnanolone 315.0	280.0	255.0	370.0	350.0	370.0	∅

Table V  
 Urinary steroid excretion ( $\mu\text{g}/24\text{ h}$ ) in the newborn, averaged for the first three days of life with no treatment and for days 4, 5 and 6 during which ACTH was administered

Infant	Treatment	Average urine volume (ml/24 h)	PREG. <sup>1</sup>	DHA <sup>2</sup>	21-OH-PREG.	16-O-AD	16-OH-DHA	16-OH-PREG.	AT <sup>3</sup>	Cortisol	Tetrahydro-group	
1	None . . . . .	290	<50	<50	190	98	1087	1460	1300	1327	<80	<40
	ACTH . . . . .	350	<50	<50	495	88	3262	4052	5088	1769	1000	1088
	% increase				160	-10	200	178	289	33	>1100	>2600
2	None . . . . .	205	<31	37	352	713	2213	1660	2460	1173	<400	<240
	ACTH . . . . .	274	91	110	285	527	1787	3240	5813	1153	2400	2733
	% increase		>300	198	-19	-26	-19	95	136	-2	>500	>1000
3	None . . . . .	31	<12	<12	436	713	2537	1887	860	680	200	<120
	ACTH . . . . .	265	18	19	711	1027	5130	5080	4653	1707	550	816
	% increase		>50	>58	63	44	100	170	441	151	161	>580
4*	None . . . . .	127	<50	<50	213	98	1320	740	920	673	<100	<70
	ACTH . . . . .	198	<50	<50	407	167	2253	1967	2827	1007	1200	632
	% increase				90	70	71	166	207	50	1100	802
5	None . . . . .	290	<50	<50	207	<70	2040	1107	2993	1467	<100	110
	ACTH . . . . .	323	<50	<50	647	75	2240	2815	5933	1393	1080	737
	% increase				213	<7	10	156	98	-5	983	570
1-5 (grand average)	None . . . . .				275	338	1847	1371	1707	1064	<170	<116
	ACTH . . . . .				509	377	2935	3430	4863	1406	>1250	>1200
	% increase**				82	>11	59	150	185	32	>600	>1000

\* For this infant, control days were 4, 5 and 6 with ACTH given on days 7, 8 and 9.

\*\* Calculated from grand totals before and after treatment.

<sup>1</sup> *P*<sup>5</sup>-Pregnenolone

<sup>2</sup> Dehydroepiandrosterone

<sup>3</sup> Androstenedione

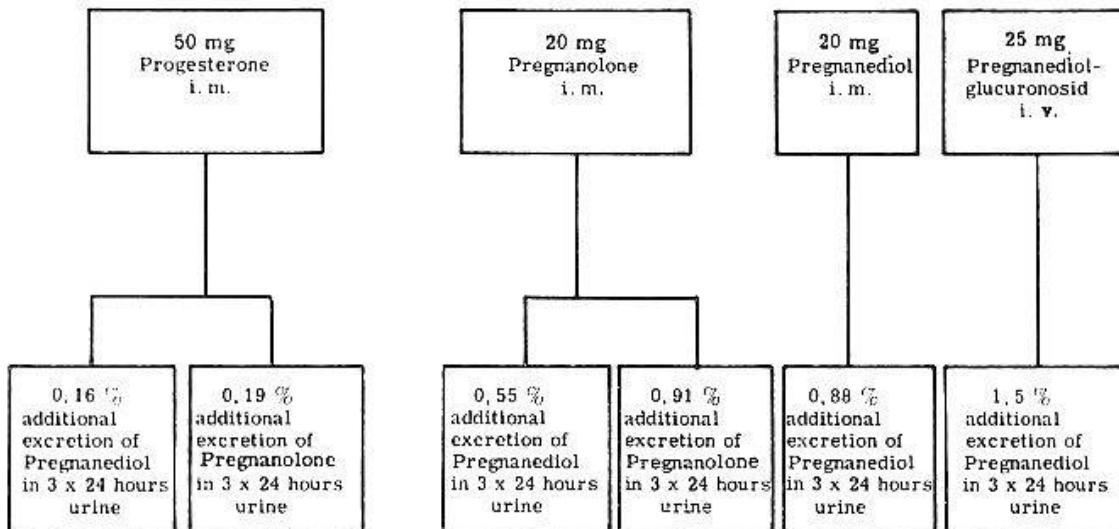
<sup>4</sup> Androstetriol

Table VI

Different level of excretion of pregnanediol and pregnanolone in the urine of suckled and not suckled newborns ( $\mu\text{g}/24\text{-hour urine}$ )

Number of determinations	Excretion of	Without mothermilk, day of life			With mothermilk, day of life			
		1st	2nd	3rd	4th	5th	6th	
12	pregnanediol pregnanolone	253.8	120.0	37.4	91.9	108.5	98.2	mean
		750.0	440.0	450.0	700.0	730.0	650.0	
12 6	pregnanediol	with artificial milk			80.1	64.2	62.1	significant $p < 0.05$
		with mothermilk			89.9	108.5	98.7	
12 6	pregnanolone	with artificial milk			410.0	396.0	361.0	significant $p < 0.01$
		with mothermilk			700.0	730.0	650.0	

Table VII



no increase of pregnanediol in 2 out of 6 cases. In the other newborns an increase up to 100% is seen, which is significant at the 0.05 level (Table IV). In 2 out of 5 cases an elevation of  $\Delta^5$ -pregnenolone up to 300% occurred. A 100–400% increase was also noted in the 16-hydroxypregnenolone fraction in all cases (Table V). A part of the former may be excreted as pregnanediol. No increase of the pregnane and pregnane derivatives and their metabolites occurred following  $3 \times 5000$  IU HCG.

Interesting enough the excretion of pregnanediol and pregnanolone was significantly higher in newborns which had been nursed by their mothers than in newborns fed with artificial milk (Table VI). Pregnanediol was found in the mothers milk on day 2, 3 and sometimes 4 in an amount of 30–55  $\mu\text{g}/100$  ml.

Intramuscular injection of 50 mg of progesterone caused an additional excretion of 0.16% of pregnanediol and 0.19% of pregnanolone in the urine



of the newborns. 20 mg pregnanolone i.m. effected an additional excretion of 0.55% pregnanediol and 0.91% pregnanolone. Intravenous injection of 25 mg of pregnanediol glucuronosid resulted in an additional excretion of 1.5% of pregnanediol. The rate of excretion is much less than in the adult (Table VII).

### Summary

The investigations have shown that the newborn produces and excretes small amounts of pregnenolone, 16 $\alpha$ -hydroxy-pregnenolone, progesterone, progesterol-20 $\alpha$  and -20 $\beta$ , pregnanolone and pregnanediol. In the first days of life, part of these steroids is supplied from the placenta or through the mother's milk. A basal excretion is, however, maintained by the newborns own endocrine glands. The excretion of the pregnene and pregnane derivatives can sometimes be stimulated by administration of ACTH and is not influenced by HCG. It is therefore probable that the steroids excreted in the urine of the newborn are produced by the adrenals. The metabolism, especially the rate of excretion in the urine, is different in the newborn from the conditions in the adult in as much as less than 1% of the substance administered is excreted.

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## Discussion

J. STAEMMLER: Wie erklären Sie, dass Neugeborene, die mit Muttermilch ernährt worden sind, eine höhere Ausscheidung an Pregnanediol hatten als die, die mit künstlicher Milch ernährt worden sind?

CH. LAURITZEN: Ich würde meinen, dass das dadurch bedingt sein kann, dass die Kinder mit der Muttermilch Steroide zugeführt bekommen, zumindest in den ersten Tagen. Es ist ja bekannt, dass in der Muttermilch  $3\alpha$ - $20\beta$ - und auch  $3\alpha$ - $20\alpha$ -Pregnanediol vorhanden ist. Das wurde mehrfach untersucht, und wir haben das selber auch nachweisen können. In der Muttermilch sind Steroide vorhanden, die möglicherweise von Neugeborenen enteral resorbiert wurden.

J. STAEMMLER: Die Werte sind hoch, die Sie da angegeben haben.

CH. LAURITZEN: Sehr hoch nicht, aber die Differenzen sind gerade signifikant:  $p < 0,05 \mu\text{g}$  für Pregnanediol und  $< 0,01 \mu\text{g}$  für Pregnanolon.

J. HALLER: I have learnt from your first Table that progesterone is excreted by the newborn to an extent which in adults, according to my information, is not excreted in that quantity but in a smaller one. Those figures which you gave are not higher in newborns compared with adults?

CH. LAURITZEN: This quantity is coming from the placenta I think.

J. HALLER: There must therefore be a difference between the excretion mechanism of the progesterone produced in the placenta and that which may be endogenous, for you also demonstrated with your 15 mg injection that the pregnanediol excretion was increased but you did not say anything about the progesterone excretion.

CH. LAURITZEN: Maybe there is a difference after the administration of progesterone as compared to the excretion of endogenous progesterone. We have, however, not studied the excretion of progesterone in the injection studies.

B. LUNENFELD: Did you find any correlation between the intensity of the icterus of the newborn and the pregnanediol excretion?

CH. LAURITZEN: We have not investigated this, but someone has. I do not remember his name, but he has told me that he had found a correlation.

H. BREUER: As far as the excretion of free progesterone is concerned I think that the values in the newborn are higher than in adults. The latest news from Edinburgh is that the excretion of progesterone varies between 1 and  $10 \mu\text{g}/24$  hours. Now I think there is a different excretion mechanism between the newborn and the adult as far as progesterone is concerned. I wonder whether you have any idea about the form of conjugates in which progesterone may be excreted in the urine of the newborn; whether this could be an enol glucuronide. The second question is what happens to the injected material in the newborn if you find only 1% in the urine? Have you any idea about the route of excretion of the metabolites of progesterone in the newborn?

CH. LAURITZEN: No. But I would like very much to know, and I think we should investigate this. Perhaps a great amount goes away with the feces. The function of the kidneys is very, very low in the newborn because the glomerular filtration and the tubular excretion are very low. I think a lot of the substance may go away with the feces or the meconium. However, I do not know exactly.

H. BREUER: I would suspect - and this is only a hypothesis - that much of the material is excreted through the skin. You know that in the newborn an excess of fluid is excreted to a great extent through the skin, and not through the kidney. This could also apply to progesterone. As far as the metabolism is concerned, probably the low activity of the glucuronosyl transferase in the newborn may be one of the factors which contributes to the high excretion of progesterone in the newborn.

CH. LAURITZEN: This is very interesting because there may be different conjugated forms.