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Opinion

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Strange linearities in human pregnancy. The immediate immense consequences for personal women's reproductive lives

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Abstract

Maternal ages categories (by 5 years of age, 15-19, 20-24, 25-29 etc.) as well as pre-pregnancy body mass index (BMI), also interestingly by categories of 5 kg/m² (15-19 kg/m², 20-24 etc..) have both linear associations with important maternal/fetal morbidities. For maternal ages: rate of cesarean sections, vaginal deliveries, active vaginal procedures (vacuum, forceps etc.), incidence of breech presentation at term, placenta praevia. For pre-pregnancy BMI, allowing to define optimal gestational weight gain (GWG) for the index pregnancy: : rate of cesarean sections, vaginal deliveries, rates of large or small for gestational ages newborns (LGA&SGA), rate of macrosomic babies (≥ 4 kg), and incidence of late-onset preeclampsia (≥ 34 weeks gestation, 80 to 90% of preeclampsia cases in a population).

Conclusion: These linear associations (biological mathematical laws?) suggest underlying biological principles to investigate. It implies immediate practical consequences: First, prediction since the beginning of any pregnancy of important maternal/fetal morbidities. Second, by calculating optimal gestational weight gain, should permit to lower these important complications. Third, because of these linearities maternal ages as well as pre-pregnancy BMI divided by increments of 5 (or as continuous variable) should be in the future included in quite all logistical models in epidemiological perinatal studies.

The problem of overweight/obesity in obstructed labour

The "adventure" began in 2005. We were with my obstetrician friend Georges Barau in the room next to the amphitheatre after an emergency caesarean section, it was around 11 p.m. at night during a call. He told me "we obstetrician have been obsessed and taught on bone-pelvis dystocia. But, nowadays, with good nutrition and disappearance of massive rickets in temperate countries, this 'bone dystocia' is no more the problem. I think that nowadays the dystocia problem might be rather due to 'soft tissue dystocia' namely the pelvis fatness. Have a look to your data and see if there is an association between BMI and rate of c-sections". If there was something, we both thought to find that the association between BMI and rate of c-section should be like a U curve; high in very lean women, relatively low in normal shaped women and then high in obese ones [1]. Our surprise was to discover that indeed it was a linear curve from "meagers" to "normal", overweight, and all kinds of obesities (class I to III). Lean women delivered vaginally better than women 20-24 kg/m² [1].

The problem of adolescent (<18 years of age) and teenage (<20) pregnancies. Another debate on obstructed labour

In Reunion island, we still had in the first decade of the 2000's (it is beginning to disappear nowadays with the important rise of the level of education in our youth the last ten years) an important problem of adolescent pregnancies (before 18 years of age): 4% of our deliveries (and 11% of our primiparas) were adolescent, very well socially accepted in Reunion island, and integrated in reunionese families [2]. We did several studies on the subject [3-5], plus or minus suggested by our health authorities who wanted to "fight the problem" and have reliable epidemiological data. We did at first our research within back mind the "Frazer seminal model" i.e. that adolescent pregnancies are a kind of catastrophy in terms of perinatal adverse outcomes [6]. We were surprised to find that, indeed adolescent mothers had twice risk of early pre-term (< 33 weeks gestation) new-borns than their 20-29 year counterparts (4% vs 2% #), but for all the obstetrical side they did much better than older primiparas [3-5], constantly with a linear rise.

#4% of early preterms means also in mirror that 96% of babies had a good survival chance in absence of modern neonatology, which was the case during 99.9% of *Homo sapiens* existence.

Then, we went further, only focusing on primiparous deliveries (these deliveries are by far much longer and "laborious" then multiparous ones) and obstructed labours (cause of several million of maternal deaths since the beginning of our species).

In another report, we found five linear trends associated with maternal ages in primiparae from 12 years to 42+. 1) vaginal deliveries without any medical intervention, "natural birthing" [7] 2) and 3) rate of caesarean sections and rate of operative vaginal procedures (vacuum,

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forceps, spatulas,) these 2 last being in mirror with vaginal deliveries. 4) spontaneous breech presentation at term was also a linear curve; if you are 18 years old, the incidence is 1.8%, if you are 35 the risk is 3.5% (the linear equation being y=0.1x) [8]. 5) Further, and finally, we tested natural occurrence of spontaneous dangerous placenta praevia in primiparas (synonymous of maternal death by bleeding without caesarean section): it is very low (quite inexistent) in very young mothers and increases linearly with advancing maternal ages.

The resultant of these findings leads to a simple equation: y= 1.4 x. [9]

(y being active medical interventions, x maternal age at birth)

Y=1.4 X means that at 16 years old at your first birth, your risk of requiring active obstetrical medical intervention is 22% , 30 years old (the current average age at first birth in Europe nowadays) 42%, at 39 years: 55%. We proposed that "These 5 consistent linear laws concerning human first births are difficult to understand without hypothesizing an underlying biological principle. Before the start of modern obstetrics, young women were condemned to begin their reproductive lives during puberty, because of absence of any type of contraception and a short expectancy of life." Indeed, during 99.8% of our species' existence (2 to 300,000 years) women have delivered with the only help of their female's friends, family, or matrons. Also, we concluded that "Primiparous women appear to be protected against maternal deaths at birth (severe dystocia by cephalopelvic disproportion, need for vaginal operative help, breech presentation and placenta praevia) at younger ages." [9]. These findings suggest then that women have been "shaped" by evolution to have their first babies at young ages, exactly like all other 4,500 mammal's species. It confirms that puberty is strictly synonymous of beginning of reproduction in all the mammalian kingdom.

It is therefore fundamental and of interest for women to know that it is probably better to have their first child before 25 years of age. Over, we become highly dependent of nowadays' modern obstetrics (namely the safety of c-section procedures, which were considered as dangerous until the 1960's).

The problem of gestational weight gain

Knowing the optimal gestational weight gain (GWG, from conception to birth) among the annual 135 million of human pregnancies is considered to be one of the "Holy Grails" to achieve for maternity health care providers and for women themselves. Extensive literature exists on the subject with, in background, the current international cornerstone which is the 2009-IOM recommendations [10] based on the WHO-BMI classification standardized in 2000 [11]: underweight women (before pregnancy) < 18.5 kg/m² should have a GWG between 12.5 and 18 kg, normal weight, 18.5-24.9 kg/m², a GWG of 11.5-16 kg, overweight, 25-29.9 kg/m², a GWG of 7-11.5 kg, and obese > 30 kg/m² a GWG of 5-9 kg. Since then a lot of controversies aroused on these recommendations (Asian people claiming that their women are leaner than Caucasians, on the other side people having a lot of obese women in their populations). We already extensively discussed these controversies in another paper [12].

Based on the simple axiom: "what is the optimal gestational weight gain at term (optGWG) to achieve the natural rate of 10% of SGA (small for gestational age) as well as 10% of LGA (Large for gestational age) in newborns in my population", we have found in Reunion island (French overseas Department in the Indian Ocean, nearby Mauritius island) the mathematical linear equation:

optGWG (kg) = -1.2 ppBMI (Kg/m²) + 42 ± 2kg [12].

optGWG being optimal gestational weight gain. ppBMI being pre-pregnancy BMI.

As a matter of fact, if we consider crude results on a reproductive population, only women with a normal BMI achieve an equilibrium in the SGA/LGA risk (both 10%). Very thin mothers have a higher risk of small for gestational age (SGA) infants, and rarely give birth to a large for gestational age (LGA) infant. While morbidly obese women often give birth to LGA infants, and rarely to SGA. This equilibrium in the SGA/LGA risk (both 10%) is materialized geometrically by a crossing point of both SGA/LGA curves. Associated with different maternal corpulences, we proposed to call this 10% -crossing point the Maternal Fetal Corpulence symbiosis (MFCS) [12].

The reflection then was to test if the corpulence of 2 separate individuals (mother and foetus) had a mutually interactive dependency concerning their respective weight, by testing the MFCS by each BMI categories 5 kg/m² by 5 kg/m². We found that there is a regular shift from the right to the left beginning with lean women towards obese ones to achieve the famous MFCS point (lean women necessitate to have a weight gain around 20 kg –vs 12.5-18, IOM-, normal shaped ones around 14 kg, overweight around 6 kg –vs 7-11.5, IOM- etc… AND severe obese beginning at 36 kg/m² should lose weight during pregnancy –vs plus 5 to 9 kg, IOM- [12]. In fact, the result is the above described linear equation. It is of note that, since it is a mathematical linear equation it allows that EACH WOMAN may be considered as a SINGLE PLOT and that we may calculate for each woman at the beginning of pregnancy her individualized optimal gestational weight gain optGWG for that pregnancy. This is of paramount importance because we no more classify women in "guilty categories" (underweight/normal weight/overweight/obese class I/obese class II). Each woman has now her personal goal to possibly achieve.

We have put an online calculator consultable on smart phone at REPERE.RE (REseau PErinatal REunion), in three languages (French, Spanish and English) [13], adapted to the Reunionese women. We encourage any reader to validate these findings adapted to their own populations (it is easy to do if you know the specific SGA/LGA curves of your term -37-42 weeks gestation- newborns).

Major practical consequences for each woman to achieve an optimal gestationalweight gain (optGWG)

First, we have recently described that increased BMI has a linear association with late-onset preeclampsia (LOP) and NOT with early onset preeclampsia ((LOP ≥ 34 weeks gestation, EOP < 34 weeks gestation) [14] (Figure 1). Early onset (EOP) is the major complication of human pregnancy with terrible maternal/fetal morbidities/mortality. Hopefully LOP is much less severe with particularly a high probability of 100% survival of new-borns. Hopefully again, LOP represents 90% of preeclampsia cases in developed countries and 70% of cases in other parts of the world [15]. Then, we thought to test if we could counterbalance the morbid effect of overweight/obesity and possibly lower the rate of LOP in a population.

We have then recently retrospectively tested the effect of achieving optGWG (± 2kg) in our reunionnese population by a mathematical simulation on an 18 -year (2001-2018) [16] and 19-year historical cohort. (2001-2019) [17] on 57,000, and then 59,000 term pregnancies.

1) The result concerning late onset preeclampsia is that we should almost halve the incidence of this disease in overweight and, moreover in all kind of obese women (class I to III), by achieving an optGWG [16].

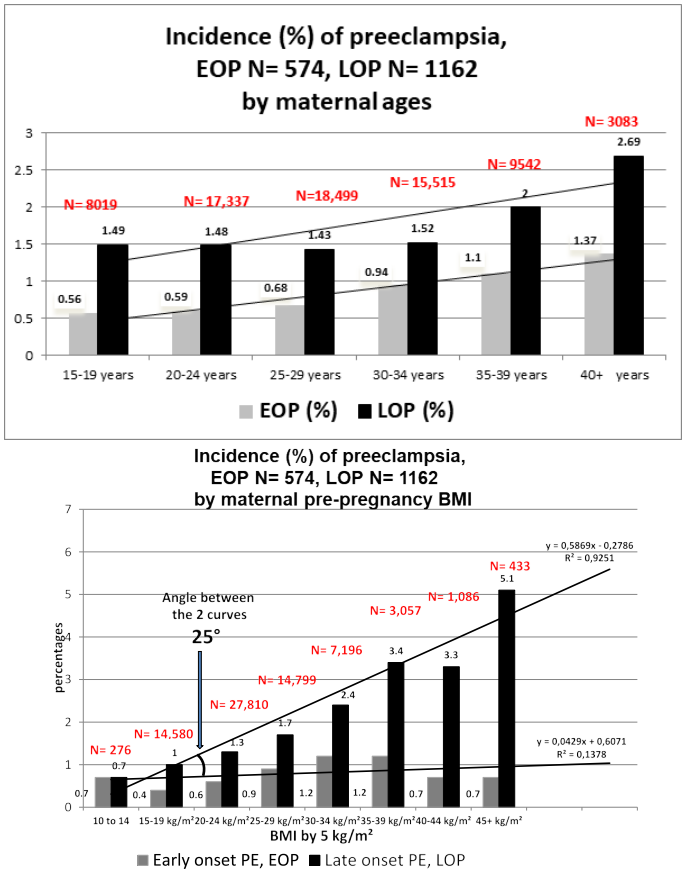

Figure 1. Different behaviours between maternal ages and maternal pre-pregnancy BMI concerning early onset and late onset preeclampsia [14].

Considering other maternal-foetal important morbidities [17].

2) The rate of caesarean sections would be diminished by some 30% in overweight-obese women

3) The rate of large for gestational age (LGA babies) would be of 10% (the very definition of the linear equation) instead of some 25% in severely obese women.

4) The rate of macrosomic babies (≥ 4 kg) would be diminished by 30 to 40% following the different gradations of severe obesities (class II and III).

5) Transfers in neonatal departments of new-borns is significantly lower for class II and III women

6) The rate of small for gestational age (SGA babies) would be of 10% (again, the very definition of the linear equation) instead of some 25% in lean women.

7) Concerning gestational diabetes mellitus (GDM), as it is a retrospective study, we could not yet show an effect: as the diagnosis of GDM is made during pregnancy around 20-24 weeks gestation the "evil" is already done at this period in case of excessive weight gain in overweight/obese women. We propose that a prospective follow-up and counselling, since the first prenatal visit (the linear equation is based on PRE-pregnancy BMI) would allow women to reach the 20th-24th week with an adequate GWG. Therefore, and mechanically, the rate of GDM would become lower in obese population.

In summary, we may have significant health (and cost) benefits by lowering c-section rates, term preeclampsia, macrosomic babies and LGA babies in overweight/obese women and low-birthweights babies in lean women.

Interesting possible difference between "maternal-age-5" AND "pre-pregnancy-BMI-5" [14]

As shown as example in figure 1, "maternal-age5" and "Pre pregnancy BMI5" with the example of preeclampsia: the well-known higher preeclampsia risk with maternal ages is equally shared for early onset EOP (< 34 weeks) and for late-onset LOP: the two curves are PARALLEL. For maternal pre-pregnancy BMI, the curves make a 25° angle. In other occasions (not shown on a figure 1), "maternal-age5" and "Pre pregnancy BMI5" are both parallel with the example of caesarean section risk [1,7].

Conclusion

In general science, it is accepted in physics for example that nature laws can be translated in mathematical models/equations. But physicists argue also that biologists are far back behind "biologist have not yet found mathematical laws to describe their science" [18]. We propose as a beginning that, in human reproduction, concerning a) maternal ages categories by 5 years of age (15-19, 20-24 etc..) and b) maternal physiological BMI (before any pregnancy), also, interestingly, by categories of 5 kg/m² (15-19, 20-24 kg/m² etc.) we have linear equations of paramount consequences. These linear equations suggest that there are some biological underlying principles, which may be interpreted as mathematical biological laws. Even not fully understood, these findings imply immediate useful and practical consequences. In the particular case of BMI as a cornerstone of safer human deliveries is the triumph of Quételet's premonition 2 centuries ago [19].

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